ROLE OF SUPERIOR COLLICULUS IN VISUAL TO MOVEMENT SPATIAL TRANSFORMATIONS DURING MEMORY-GUIDED AND REACTIVE HEAD-UNRESTRAINED GAZE SHIFTS

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Abstract

The fundamental process in the brain which allows the generation of what is known as behavior, is the transformation of sensory or internally generated information to commands for movement. For example, shifting the line of gaze to look at and interact with our environment requires transformation of visual information into proper contraction of eye and neck muscles. In this thesis I studied the transformation of visual signals to movement commands in the primate's superior colliculus, a key structure in sensory integration and gaze movement generation. In the first chapter the frames of reference and the spatial information encoded by the visual and motor activity of superior colliculus, in different neuron types, are investigated in a memory delay task, and the results provide support for visuomotor transformation process that occurs between and within neurons during the memory delay task. In the second chapter the focus of study is on reactive gaze shift task and we show that the spatial information occurs during the burst of activity of single neurons even in such a short interval and without a presence of a memory delay. In the last (third) chapter, I compared the visual and motor spatial coding and their transformation between the reactive and the memory delay tasks and found that although similarities exist, there are important differences in neural activity profiles and the spatial codes and the extent of visual to movement transformation. Together the findings in this dissertation suggest that the process of visual to movement transformation occurs between and within neurons in SC regardless of the duration of the gaze shift or the task, however task demands influence both the activity and spatial coding of neurons which are consequently translated in the differences in behavior in each task

Dedication

I dedicate this dissertation to my beloved wife, Elham, who so patiently supported me through my graduate education and was always encouraging me to continue through some of the most difficult times of my life, without her I would not have been able to pass through these challenging obstacles. I appreciate all your amazing help, your unconditional love and your heart warming words.

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Table of Contents

List of Figures

Chapter 1: General Introduction

Movement is an integral component and a manifestation of life. From the chemotaxis movement of singe cell organisms along the chemical gradient, to the carefully coordinated movements of a gymnast, movement can serve very diverse goals and purposes. Although many body movements—especially in primates—are generated by internal and cognitive processes, such as climbing a tree or dancing, however, various sensory stimuli also elicit behaviours in the form of purposeful movement, such as moving the eyes and head to align the gaze to a sudden visual or auditory stimulus, or reaching and grasping to obtain food from the environment. In primates, as movements become more complex and coordinated, greater areas of the brain are involved in learning, planning, and generating the movements. In addition, more than half of the areas in the brain are involved in aspects of processing visual information. This enables the complex interactions necessary to link visual information with movements. This dissertation explored an important aspect of this interaction involving how visual information is encoded and transformed to signal eye and head movements. To study these phenomena, we recorded the single-unit activity of neurons in the midbrain's superior colliculus (SC), which is a key brain structure involved in the generation of oriented movements during gaze shifts in different behavioural contexts, and analyzed these responses to specify the transformation of spatial information in the structure.

1.1 Saccades (Behavioural Aspects)

Combined, coordinated eye and head movements, also known as gaze shifts, are used routinely to achieve different goals. These movements range from reflexive rapid eye movements

(i.e., saccades, to respond to a stimulus that unexpectedly appears in our visual field) to voluntary changes in gaze shift to explore the environment. The purpose of saccades is to relocate the visual stimulus of interest on the fovea (the region on the retina with the highest density of cone receptors), which results in high visual acuity that provides fine details of the visual stimulus(Schein 1988). Identifying stimuli is essential for obtaining basic needs for survival, avoiding danger, and seeking food, and also at a more complex level, for attention and communication purposes. Gaze movements are therefore extremely important for purposeful and efficient interactions with the outside world, and thus the circuitry that controls them has been well conserved throughout evolution(Fuchs 1976). Saccades have some fundamental and consistent characteristics regardless of the purpose and setting of their execution (Tweed and Vilis 1990). However, the setting can have a major influence on saccadic parameters; for example, the reaction time of saccades has a distinctive pattern under different circumstances. This variation suggests that different neural pathways are involved in each of the saccade subtypes and in the tasks in which saccade is used. For example, in situations when saccades are directed to locations in space that were recently explored, the subsequent saccades to the same location have significantly longer reaction times, which is a phenomenon known as inhibition, and reflects the influence of attention circuits on saccades (Goldberg and Wurtz 1972, Goldberg and Bushnell 1981, Schall 2004). Similar influences have been reported in visual search tasks, with varying reaction times based on variations in task difficulty, as well as the repetition of the task, which reflects the effects of the decision making process and practice on the gaze system (Schall 1995, Krauzlis, Liston et al. 2004, Krauzlis, Lovejoy et al. 2013). Velocity and accuracy of the saccades are other important characteristics that are often altered by changes in the type of saccade. The

accuracy is defined as the difference between the saccade end point (i.e., line of gaze), and the actual location of the target. This is influenced by several task demands (Kapoula and Robinson 1986). For example, when saccades are made to remembered locations rather than visible targets, the magnitude of the inaccuracies increases. Similarly, the magnitude of errors is influenced by the demand to make saccades in relatively shorter times (i.e., the speed–accuracy trade-off) and the presence of distractors (Schall 1995, Schall 2004, Chatham and Badre 2015). Most saccades have both vertical and horizontal components, which are coordinated in terms of amplitude and velocity by appropriate contributions of different brain nuclei to result in an oblique saccade and keep the saccadic trajectory nearly straight. Given a simultaneous start of the horizontal and vertical components, this requires temporal stretching of the component with smaller amplitude so that the trajectory of the oblique saccade does not have a curvature. Thus, the duration of the shorter component is positively correlated with the amplitude of the longer component. These relationships make it possible to predict, with reasonable accuracy, the duration and peak velocity of a saccade as well as the shape of the velocity profile given only information about either the movement amplitude and direction, or, alternatively, the locations of the visual targets, because the vector of a saccade is correlated with target displacement(Freedman and Sparks 1997, Freedman 2008).

1.2 Eye-Head Coordination during Gaze Shifts

Saccades are often made in combination with coordinated head movements, which together shift the line of gaze onto the stimulus of interest. In primates, the range of eye movements is approximately ±40°, so any movements to stimuli within this 80° region can be achieved by eye movements alone, with larger movements requiring accompanying head

movements. Gaze shifts usually start with a rapid change of eye position relative to the head, and head movements start at a relative delay, the end of gaze shift is when the line of sight is directed toward the visual target. At this point, the eyes are fixed on the target, but the head usually continues the movement for a short period of time (Freedman 2008). During this latter continuation of head movement, the eyes move in the opposite direction with a speed similar to that of the head movement, so the line of sight does not move. Despite the apparent delay in head movement during gaze shifts, electromyography studies have demonstrated that there is an increase in agonists (and decrease in antagonists) during neck muscle tension, which interestingly begins prior to the increase in eye muscle contraction. This is presumably due to the need to overcome the significantly higher inertia of moving the neck and head compared to that of moving the eyes, suggesting that the signals required for head movements may first be transmitted to the nuclei responsible for neck muscle contraction, and thereafter to the oculomotor nuclei (Bizzi, Kalil et al. 1972, Zangemeister and Stark 1981, Corneil, Olivier et al. 2002, Corneil, Olivier et al. 2002). Nevertheless, the findings of several studies regarding the close relationships and covariance of eye and head movement velocities, latencies, and trajectories suggested that there is a common initial movement command for the eyes and head, which may subsequently divide to the appropriate downstream motor nuclei (Guitton, Munoz et al. 1990, Galiana and Guitton 1992). Despite these findings, the relative coupling of eye and head movements rely on several factors, such as the predictability of location and timing of the visual targets (Bizzi, Kalil et al. 1972), movement amplitude (Barnes 1979, Freedman and Sparks 1997, Freedman 2008), initial position of the eyes in the orbit (Freedman 2008), and the likelihood of head movements (Fuller 1992, Fuller 1996, Stahl 1999). Despite the possible common initial

command of eye and head movements, these signals can be separated depending on the task demands (Figure 1.1). For example, when the amplitude of gaze shifts increases, the difference in time between the saccade and head movement onset decreases so that these two movements occur almost simultaneously (Freedman and Sparks 1997). Consequently, the concurrence of eye and head movements is largely task-dependent and variable. Normally, during small amplitude gaze shifts, the head movements lag behind the onset of eye movements; however, during larger gaze shifts or gaze shifts toward predictable target locations, head movements occur at the same time, or even prior to the onset of the saccades. Moreover, electrical stimulation of the omnipause neurons delays the saccade onset without changing the onset of head movements, which further suggests that at some point signals for eye and head movements are separated from their common initial command and become independent (Freedman 2008, Chapman and Corneil 2011). Another example of task demand influences is the predictive versus triggered nature of movements. In the former, saccades have a lower peak velocity, longer duration, and larger head movement (Bizzi, Kalil et al. 1972, Monteon, Avillac et al. 2012).

Another aspect of eye and head coordination is the occurrence of the vestibulo-ocular reflex (VOR) and cervico-ocular reflex, which together stabilize the visual image on the retina during head movements. Information on head velocity comes from the semi-circular canals and is used to generate eye movements with matching velocities but in the opposite direction, so that the retinal image has a net speed of zero and is thus perceived as stable (Freedman 2008). In theory, two competing signals exist for determining the eye velocity: one originating from the saccadic command and the other from the VOR regarding the matching head velocity. Because of the ultimate goal of stabilizing the retinal image, the VOR signal overrides the saccade velocity

signal and the final eye velocity should not exceed the head velocity. However, in various studies where subjects made large gaze shifts (~30°) (Roucoux, Guitton et al. 1980, Jurgens, Becker et al. 1981, Tomlinson and Bahra 1986), the eye velocity exceeded the head velocity. Thus, the VOR is essentially turned off during larger gaze shifts. In contrast, during smaller gaze shifts, the VOR remains active and thus contributes to corrections of the retinal image, because the change in the line of gaze due to the head movements is negligible (Blakemore and Donaghy 1980, Tomlinson and Bahra 1986, Freedman 2008). It is likely that the VOR gain is modulated in relation to the motor error. During larger gaze shifts in the early movement period, when the head velocity is peaking and the contribution to the gaze shift is maximal, the gain is low; the gain then increases toward the end when the head velocity decreases (Pelisson and Prablanc 1988). Based on the previous hypotheses for eye and head movement signals, together with the implications of the VOR, it is probable that the interactions between head and eye signals subsequently lead to their dissociation in metrics and kinematics. Thus, a new model is proposed involving signals that are added after the common gaze (i.e., eye + head movements) command is dissociated, to modulate the head and eye velocities depending on the amplitude and starting positions of eye and head components (Freedman 2008). One example of a similar circuit is the nucleus reticularis gigantocellularis (NRG), which receives direct inputs from the SC and outputs projections to the neck motor neurons (Cowie and Robinson 1994). Stimulation of the NRG results in pure horizontal head movements without any saccadic component when the eyes fixate on a target. However, during gaze shifts, the stimulation of the NRG at different frequencies and timings leads to subsequent reductions and changes in the peak velocity profile of eye movements, which are similar to the changes in eye velocity during increasing head amplitudes (Quessy and Freedman

2004), thus supporting the model that the head movement signals are able to modulate the saccadic burst generators downstream of the common gaze commands.

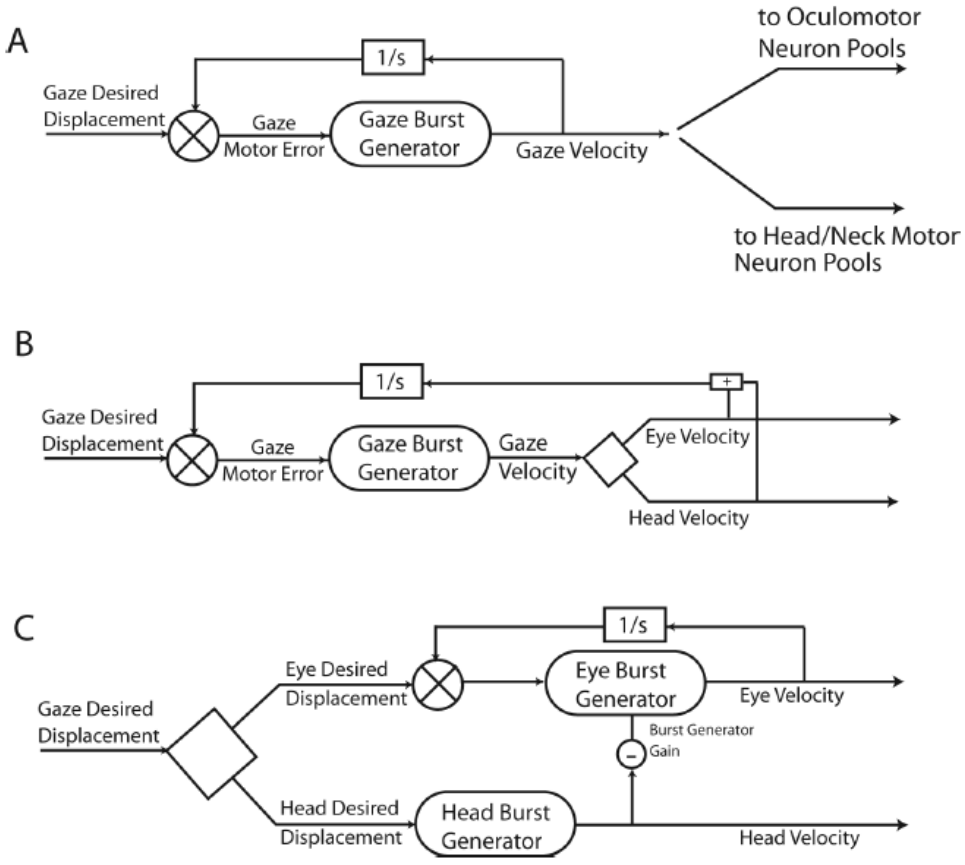

Figure 1.1. Schematic diagrams of three different proposed models for coordinated eye and head movements. A) The panned gaze displacement is compared with an ongoing estimate of the current displacement to calculate a gaze motor error signal. This signal is the common origin of signals for both eye and head movements. B) The gaze velocity signal is first divided into separate signals for eye and head movements in a dynamic feedback loop mode. C) The division of separate eye and head signals occurs earlier in the control loop. There are separate eye and head velocity signals for each effector's displacement. The gain signal from the head movement provides feedback to adjust the eye signal (Freedman 2008).

1.3 Issues in eye and head movements in three dimensions

Eye and head movements have three separate but related components: horizontal (along the vertical axis), vertical (along the horizontal axis), and torsional (along the orientation axis) (Crawford, Henriques et al. 2011). Three-dimensional movements create the problem of increased degrees of freedom, so that various eye and head orientation possibilities are considered, which is further complicated by the non-commutative nature of rotational movements (i.e., the order in which the sequence of the rotations occurs affects the final intended orientation) (Tweed and Vilis 1987, Tweed, Haslwanter et al. 1999). Moreover, there is only a specific combination of orientation components, regardless of the initial gaze orientation, for a given gaze direction (Donder's Law). The three-dimensional orientation therefore remains constant for a given horizontal and vertical angle (Tweed and Vilis 1990). Donder's Law is usually true for isolated eye movements, but head movements are restricted by Fick coordinate systems, where head movements are defined in the specific order of horizontal, vertical, and torsional components (Crawford, Martinez-Trujillo et al. 2003) (Figure 1.2). These issues have not been addressed adequately in the models mentioned above, and require the identification of further neural control mechanisms for generation and control in three dimensions.

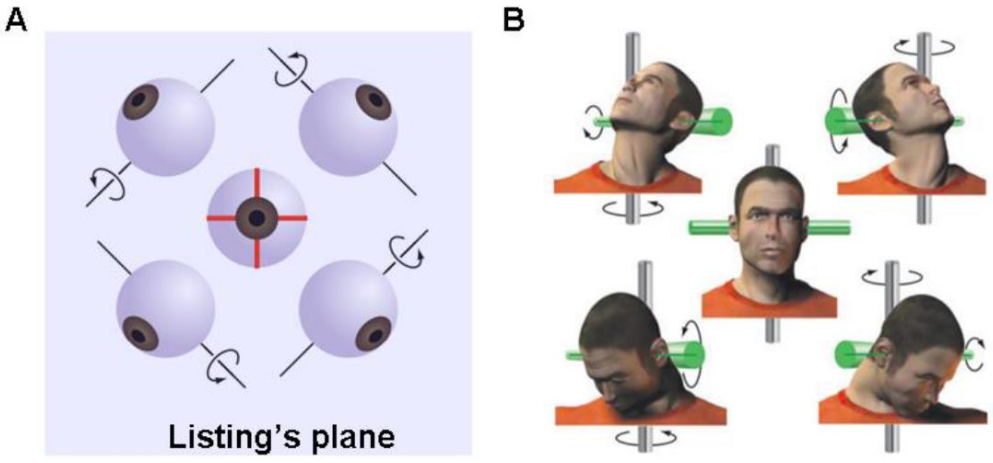

Figure 1.2 A) Schematic diagram of Listing's Law. Various possible eye orientations achieved by different torsional eye movements (back arrows) from a single initial eye position (centre) B) Illustration of Fick strategy in head Movements. Head movements occur along the body at fixed vertical (arrows along the grey rods) and horizontal (arrows along the green rods) axes (Crawford, Henriques et al. 2011).

1.4 Cortical and Subcortical Networks for Gaze Control

1.4.1 The Brainstem Circuit

1.4.1.1 Motor neurons and extraocular muscles

To describe the pattern and flow of signals that occur in the brain stem to move the eyes to the desired location, it would be beneficial to start with the output level, because the numbers of signals and neuron types at this level are relatively simpler, and then consider regions farther upstream. Movement of the eyes in three dimensions is achieved by synergistic activity of three pairs of muscles for each eye (Sparks 2002). Superior and inferior recti muscles control vertical movement, medial and lateral recti muscles control the horizontal component, oblique muscles control two-dimensional movements, and the torsional movements are controlled by synergistic activity of superior/inferior recti and oblique muscles (Suzuki, Straumann et al. 1999). The pool of motor neurons that mono-synaptically control the eye movements are found mainly in the third cranial nerve (oculomotor) and in the fourth and sixth cranial nerves (trochlear and abducens). The activity patterns of these neurons are similar because, 1) the duration of the neural discharge is approximately equal to the duration of ipsilateral saccades, 2) for contralateral saccades, if the muscle controlling the saccade is antagonist, then the neuron is completely silent, and 3) during fixations, these neurons fire tonically at a rate that is proportional to the eye position (Schiller 1970, Fuchs and Luschei 1971). The control of purely horizontal or

vertical saccades can be explained by the properties of the motor neuron firing patterns; however, there are two instances in which the eye movements require a more complicated cooperation between different motor neuron pools to achieve the desired saccade. The first of these is oblique saccades with unequal components. Because the observed trajectories of the oblique saccades are straight and not curved, and thus the vertical and horizontal components should be coordinated and cannot be entirely independent. Therefore, to produce straight oblique saccades, the beginning of the burst for each component is synchronized but the firing rate for the component with a smaller amplitude is smaller, and the burst duration longer, so that the offset of activity for the two is also synchronized (Smit, Van Opstal et al. 1990) (Guitton and Mandl 1980, Scudder, Kaneko et al. 2002, Sparks 2002). The second situation is torsional eye movements. Assuming that the head is stationary during eye movements, the neural control of eye rotations should obey Donder's and Listing's laws. These laws state, respectively, that for any orientations of eye movement the rotation values of the eyes are the same and are equal to zero. In situations with a significant torsional component, such as when the head is moving during saccades, different pools of neurons are activated in order to rotate the eyes in the desired direction (Crawford and Vilis 1992, Sparks 2002). Upstream regions which innervate the oblique and superior/inferior muscles are activated, and neurons in the interstitial nucleus of Cajal (INC) fire to keep the eyes in that rotation (Fukushima 1987, Crawford, Cadera et al. 1991, Kokkoroyannis, Scudder et al. 1996, Klier, Wang et al. 2002). Therefore, a given pattern of activity in the pontine and midbrain reticular formations (described below) recruits the appropriate motor neurons to rotate the eyes in a specific direction.

1.4.1.2 Pontine reticular formation

Before discussing how the midbrain and brainstem regions send signals to motor neurons for eye movements, it is important to describe different types of signals in the region. The two components of MN activity are the pulse and step commands, and different groups of neurons provide these inputs to MNs. The neurons in the para-median pontine reticular formation (PPRF) fire in relation to horizontal saccades, but different populations of neurons make different contributions (Cohen and Henn 1972). The trigger signal from the SC inhibits the firing of omni pause neurons (OPN), which are tonically active during fixation to inhibit unwanted eye movements. When the OPN are inhibited, the excitatory burst neurons (EBN) and the long lead burst neurons (LLBN) discharge at a high rate prior to the vertical saccades, but the LLBN burst is not as tightly coupled with saccade onset as are the EBN, and its output is to drive the EBN burst. EBN bursts in turn are mono-synaptically connected to motor neurons that control the eye muscles, and also to downstream inhibitory burst neurons (IBN), to prevent antagonist muscle contractions. This is the "pulse" command for horizontal eye movements, which is intended to overcome the viscosity of the eyeball and initiate the movement. In addition, the EBN provides the input for neurons of the nucleus prepositus hypoglossi and the medial vestibular nucleus, which are tonically active after the eyes move to the new location. These provide the "step" command, which overcomes the elasticity of the eye muscles and keeps the eye in the desired position (Robinson 1964, Sparks 2002).

1.4.1.3 Midbrain reticular formation

Neurons in the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF) provide the pulse and step commands for vertical components of saccades using a similar pattern of commands coming from the LLBN, IBN, OPN, and IBN as described above. The step command is generated by tonic activity of the neurons in the INC and the vestibular nucleus (King and Fuchs 1979, Scudder, Kaneko et al. 2002).

1.4.1.4 Brainstem contributions to head movements

Most current evidence suggests that the command for coordinated eye and head movements is generated as a gaze displacement signal by the SC, and is then transferred to separate eye and head movement pathways in the brainstem. Cowie and colleagues (Cowie and Robinson 1994, Cowie, Smith et al. 1994) investigated some of the brainstem areas that receive dense inputs from the SC and send output to cervical spinal cord regions, which are responsible for the control of neck muscles. One of the important areas is the medullary reticular region (the gigantocellularis nucleus). Microstimulation of this region induced brief head movements to the ipsilateral side. These movements were modulated by initial head positions and active visual fixation. Some stimulation generated bilateral neck contractions that appeared to stabilize the head, which could be used during gaze fixation or to terminate a gaze shift. These studies also reported that the postarcuate and precentral frontal cortices send projections to this region, suggesting that these areas contribute to volitional, and thus behavioural, movement control (Roland, Larsen et al. 1980). More recently, Quessy and Freedman (Freedman and Quessy 2004) reported that stimulation of the gigantocellularis region also cause ipsilateral head rotations in

the horizontal plane. In contrast to the findings of Cowie and Robinson, these movements accompanied eye counter-rotation regardless of whether the movements were evoked in the dark or during active fixation. The study also reported that the metrics of head movements depended on the parameters of the stimulation, but the relationship between peak head velocity and amplitude remained consistent across all stimulation sites and parameters.

Another brainstem region involved in head movements is the INC. Electrical stimulation of the INC leads to head tilt in the contralateral direction, and the pharmacological inactivation of the INC causes a characteristic contralateral tilt (Fukushima 1987, Peterson and Peterson 1987, Crawford, Cadera et al. 1991, Klier, Wang et al. 2002). Anatomical evidence has also suggested that the INC sends direct output to rostral regions of the pontine reticular formation for the control of neck muscles (Fukushima 1987).

1.4.2 Basal Ganglia

The basal ganglia (BG) are the aggregated nerve cell nuclei located just underneath the cerebrum, and are essential components of the circuitry for voluntary control of body movements. This conclusion resulted from the clinical observations that patients with BG lesions have various movement disorders involving the inability to initiate a movement to the inability to inhibit unwanted movements(Langston, Ballard et al. 1983, DeLong 1990, Redgrave, Rodriguez et al. 2010). BG disorder patients also have timing errors in their saccades (Rascol, Clanet et al. 1989). Saccades abnormalities include errors in the frequency, direction, and the timing errors as well as increased latencies of the saccades in pro- and anti-saccade tasks, and also affected the performances of visual and memory delay saccades (Everling and Fischer 1998, Leigh and

Kennard 2004, Gooding and Basso 2008). The functionally separate parts of the BG are: the caudate nucleus (CD) and putamen (PUT) (collectively called striatum), the globus pallidus, substantia nigra, and the sub-thalamic nucleus (STN). The globus pallidus is divided into the external (GPe) and the internal (GPi) compartments, and the substantia nigra is divided into the pars reticulata (SNr) and pars compacta. The CD and PUT are the input sites, receiving signals from an extensive area of the cortex and parts of the thalamus, and the GPi and SNr are the two major output areas, sending signals to some areas in the thalamus and the brainstem motor regions. Signals coming from the SNr have direct control over saccades by providing direct inputs to the SC, and indirect control over cortical regions such as the frontal and supplementary eye fields (FEF and SEF) via the thalamus (Hikosaka, Takikawa et al. 2000). The tonic GABAergic activity of the SNr neurons inhibits the SC and thalamus and therefore affects facilitation and suppression processes by decreasing and increasing its activities, respectively. The CD is the oculomotor region of the striatum, which has inputs from almost all cortical areas and involves the thalamus and GABAergic outputs to downstream regions (Hikosaka, Sakamoto et al. 1989, Hikosaka, Sakamoto et al. 1989). The CD output neurons are usually silent, but show an event-related increase in their activity in monkeys depending heavily on the quantity of reinforcement obtained after each successful saccade (Lauwereyns, Watanabe et al. 2002, Hikosaka, Nakamura et al. 2006). Two general classes of projecting neurons exist in the CD: those that directly project to the SNr and suppress their tonic activity, with the end result being facilitation of saccades (Nakano 2000), and those that project neurons, which innervate the GPe and, as a result, activate SNr neurons by decreasing the inhibitory effects of the GPe on the SNr and the STN glutaminergic neurons that have excitatory connections to the SNr (Parent and Hazrati 1995). The visuomotor

CD (Hikosaka, Sakamoto et al. 1989, Hikosaka, Sakamoto et al. 1989) neurons are clustered in a region posterior to the anterior commissure where the head representation is merging with the body representation. The majority of this region receives input from the FEF and SEF as well as inputs from the dorsolateral prefrontal cortex. Similar to the SNr neurons, CD neurons also have response fields (visual and motor), which largely represent contralateral fields. The visuomotor activities of this region are largely context-dependent and the changes in behavioural circumstances of the saccades modulate their responses. For example, activity is enhanced when the stimulus must be attended to or its location remembered, or when the goal of the saccade is retrieved from the working memory. The close similarities of activity modulations in the SNr and CD further suggest that visuomotor information is transmitted from the CD to the SNr. The PUT, another main input region of the BG, is linked to control of skeletal muscles (Stanton, Goldberg et al. 1988, Alexander, Crutcher et al. 1990). However, the extent of its input from the FEF and its direct projections to the SNr suggests that it might be involved in saccade control (Stanton, Goldberg et al. 1988, Parent and Hazrati 1995). Nevertheless, an important functional difference between the PUT and CD is the distinct spatial versus temporal accuracy of the saccades, which was suggested by studies using a paradigm that facilitated the dissociation of the two by changing the parameters of the peripheral visual stimuli (Gagnon, O'Driscoll et al. 2002). PUT activity is increased when the temporal aspect of the visual stimuli is predictable. In contrast, CN activity is enhanced when the spatial information regarding the stimuli is predictable. However, recent neurophysiological data from alert monkeys disagrees with such a strict dissociation in the PUT and CD by findings that suggest that saccade-related neurons in the CD send signals concerning temporal information prior to the appearance of a visual stimulus of spatial information after the

stimulus appears (Watanabe and Munoz 2009, Watanabe and Munoz 2010, Phongphanphanee, Marino et al. 2014). Lastly, the STN influences BG output directly by glutamatergic projections to the SNr and indirectly by excitatory neurons in the GPe, which in turn sends GABAergic projections to the SNr. The STN receives GABAergic input from the GPe in the form of feedback and direct cortical glutamatergic input from the frontal cortex (Parent & Hazrati, 1995; Smith et al., 1998; Sato et al., 2000a), including the FEF and SEF (Huerta, Krubitzer et al. 1986, Huerta and Kaas 1990, Nambu, Tokuno et al. 2002). A potential role of the frontal cortex connections may be to activate SNr neurons and immediately suppress actions in response to some changes in the surroundings (Aron, Durston et al. 2007, Isoda and Hikosaka 2008). In summary, the BG exerts control over the saccades in two different ways: 1) It contributes to the initiation of saccades by removing the sustained inhibition (i.e., disinhibition), by phasic firing of CD neurons and thus inhibition of the SNr. It is important to note that because the information relayed in the BG is usually based on memory and expectation, the BG contribution to initiation of the saccades is largely based on these two factors. Many neurons in the BG are preferentially active for memory-guided saccades, and inactivation of the BG leads to large deficits in memory-guided but not visually guided saccades. 2) The BG also has a role in the inhibition of unwanted saccades, which involves the GPe and the STN. The combined result of this pathway is an elevation in activity of SNr neurons and therefore increased inhibition of the SC. Some neurons in the GPe and STN have enhanced activity in instances that require higher inhibition, such as in sustained eye fixation or prior to a goal-directed saccade. Collectively, the two major mechanisms select an appropriate and purposeful saccade based on particular behavioural contexts and recent experiences (Hikosaka, Takikawa et al. 2000, Watanabe and Munoz 2011, Coe and Munoz 2017).

1.4.3 The Cerebellum

Various regions of the cerebellum contain Purkinje type cells that discharge in response to different types of eye movements. The majority of cerebellar areas are involved in smooth muscle pursuit and the vestibule-ocular reflex, such as the flocculus-paraflocculus complex and the nodulus/uvula (Their 2010). One of the areas that fires in relation to saccades and is also well understood is the posterior vermis, which contains the verbal lobuli VI and VII that are collectively referred to as the oculomotor vermis. This area was first identified by clinical observations that unilateral lesions to the vermis result in a reduction in the frequency of saccades as well as dysmetria (Aschoff and Cohen 1971, Ritchie 1976). The oculomotor vermis outputs are sent to the caudal fastigial nucleus that in turn sends signals to brainstem saccade generators (Yamada and Noda 1987). One suggestion is that the nature of the signals accounts for deviations in initial eye positions. Assuming such a command does not exist in the brainstem, for a successful saccade vector to be generated, there is a need to overcome the elastic force of the eye muscles when the initial eye position is not at the centre (Robinson 1981). Thus, the vermis signal compensates for eye position-dependent changes in opposing/facilitating elastic forces (Thier, Dicke et al. 2002). However, not all cells in the vermis encode for eye positions; only approximately 10% are involved, and most of the cells can be placed on a continuum between eye position activity and saccade-related activity. These saccade-related activities could send a signal for compensation of velocity-dependent viscosity, which must be overcome by the brainstem saccade generators. The duration and velocity of the brainstem firing is proportional to the amplitude of the resulting saccade, and the changes in orbital viscosity lead to changes in the intended velocity signal, which ultimately result in saccade dysmetria. The compensatory signal from the cerebellar vermis may

therefore provide compensation for the brainstem pulse duration and the appearance of normometric saccades. Thier and colleagues (Thier, Dicke et al. 2000) reported that the population duration of the firing of Purkinje cells in the oculomotor vermis was tightly linked to saccade duration. More precisely, the time of the decline of the population burst was correlated with the end of the saccade, whereas the duration and onset were not as closely related (Thier, Dicke et al. 2002).

1.4.4. The Parietal Lobe

One of the areas in the parietal lobe that has been shown to have a major role in different aspects of gaze control is the lateral inter-parietal (LIP) area located in the posterior parietal cortex. Neurons in the LIP area respond to the onset of a visual stimulus with a burst of discharge and to a burst in response to a saccade onset, as well as to discharges during the intervals between the above-mentioned discharges (Andersen, Essick et al. 1987, Blatt, Andersen et al. 1990). There are several important aspects of the different phases of activity (visual, memory, and saccade) in LIP neurons: 1) most LIP neurons with saccade-related activity have a pre-saccadic period of activity that peaks at the saccade onset, 2) the LIP activity is spatially tuned but the tuning is relatively broad compared to other visuomotor areas, 3) the spatial preferences of the three phases of activity are approximately aligned, 4) the post-saccadic activity is temporally separated from these phases and probably reflects other aspects different from post-saccadic activity, 5) saccade-related activity is related to the intended saccade and is not dependent on the presence of a visual stimulus, and 6) all three phases are modulated by eye position, which has been described as a gain field (Andersen, Essick et al. 1987, Andersen, Bracewell et al. 1990, Blatt, Andersen et al. 1990). The LIP neuronal activity is related to various

aspects of gaze control other than initiation, and motor commands are sent according to saccade kinematics, which are based on the following: 1) the saccade-related activity of many LIP neurons is much longer (average, 210 ms) than the duration of the saccade itself, 2) there is very little modulation in the firing rate during the saccades with different vectors, 3) studies have failed to find neurons in the LIP area with a purely motor response (such as those in the SC or FEF), and 4) all the pre-saccadic activities have an accompanying visual response (Barash, Bracewell et al. 1991). However, Barash et al. (Barash, Bracewell et al. 1991) found that there is an increase in the baseline activity of memory-guided saccades and the peripheral attention tasks. In both tasks, there is anticipation of a visual stimulus presentation in the receptive field that required a response. This build-up of activity prior to stimulus onset could reflect the voluntary direction of attention to the location where a behaviourally relevant visual stimulus is anticipated, involving a possible role of the LIP area. Furthermore, LIP neuronal activity has been linked to detecting salient spatial locations, such that the area of the visual field associated with the greatest activity in LIP areas corresponding to the locus of visual attention. This acts as a winner-take-all phenomenon in a manner where the LIP activity correlates better with the probability map that a given location will win the saccadic target (Desimone and Duncan 1995, Goldberg, Bisley et al. 2002, Ipata, Gee et al. 2009, Bisley, Mirpour et al. 2011). Lastly, the updating mechanism encoded by LIP neurons provides a mechanism for keeping accurate representation of spatial information, which is necessary for the control of eye movements, particularly in situations where acquisition of the exact target location may not be possible. The coexistence of an accurate place code, eye position information, and an updating mechanism for target spatial representation provides gaze-centred spatial information, which is a reference frame used by many visuomotor areas

involved in saccade initiation that is the key to successful execution of gaze (Duhamel, Colby et al. 1992). All these findings support the possibility that the LIP area is involved in the representation of space, visual localization, visuomotor transformations, and the planning of saccades, rather than gaze control commands.

1.4.5 The Frontal Lobe

The frontal lobe, amongst many other functions, is responsible for controlling voluntarily body movements, which include gaze shifts. Most important areas of the frontal lobe that have been shown to have major roles in contributing to different aspects of gaze shifts involve the anterior cingulate cortex (ACC), supplementary eye fields (SEF), and FEF.

1.4.5.1 The ACC

The cingulate cortex has long been considered a component of the limbic system in most brain anatomy reviews (Vogt, Finch et al. 1992). It corresponds to a large and rather heterogeneous region of the cerebral cortex that can be divided based on morphology, connections, and functional characteristics (Paus, Tomaiuolo et al. 1996). Many recent observations suggested that the ACC is involved in oculomotor function. Anatomical studies in monkey brains have provided evidence of dense, reciprocal connections between the ACC and the SEF (Rizzolatti, Gentilucci et al. 1990) and a relatively weaker connectivity with the FEF (Huerta, Krubitzer et al. 1987). In addition, saccades can be evoked by microstimulations in upper regions of the ACC, which are immediately ventral to the SEF. Based on recent studies, the functional classification of the ACC also needs to be reconsidered. For example, fMRI studies in humans have

reported an increase in the blood-oxygen-level dependent (BOLD) signal with increased demand in target detection (Petersen 1988) or in cases where the task requires divided attention (Corbetta, Miezin et al. 1991). Posner and Petersen (Posner and Petersen 1990) therefore suggested that the ACC is involved in response selection rather than in a direct involvement in the generation of a response. Data from neurophysiological studies involving delayed-saccade tasks reported that cells in the ACC are responsive to the presentation of stimuli in a preferred location [i.e., the response field (RF)], and they remained active during the delay period, while some cells were also active in response to the onset of movement (Niki and Watanabe 1976). The same investigators found cells in the ACC that are responsive to trials in which an error has occurred. The investigators also reported that an absence of activity of the ACC cells predicted trials in which the monkey would make errors. The original source of such error-related signals seem to be centred in the ACC; however, it is likely that it arises from a supplementary motor area, because the two regions are reciprocally connected (Garavan, Ross et al. 2003, Ito, Stuphorn et al. 2003). Similarly, some populations of ACC cells are responsive to reinforcement or reward delivery. In the population of reinforcement-related neurons, some cells are active in the same manner as the closely related SEF cells, and respond to both signals related to reward delivery (such as a tone indicating a juice reward) and to the reward itself. But some reward-related cells showed characteristics exclusive to the ACC. These neurons responded to the delivery of the reward, both when it was expected and when it was unexpected (Schall and Boucher 2007). This pattern of activity is very similar to dopamine neurons in the brainstem, suggesting that the ACC may be involved in signalling the

properties of the reward and may play a role in dopaminergic learning (Holroyd and Coles 2002, Schultz 2007).

1.4.5.2 The SEF

The SEF is a region located in the dorsomedial frontal cortex which can be considered as an oculomotor extension of the supplementary motor area. Neurons in the SEF are responsive to both visual and auditory stimulation, and some neurons in the SEF discharge in response to gaze onset (Schlag and Schlag-Rey 1987, Schall 1991). Other higher order functions have also been linked to SEF activity such as conditional motor learning (Chen and Wise 1995), object-centred representation (Olson and Gettner 1999), antisaccades (Schlag-Rey, Amador et al. 1997), sequential saccades (Lu, Matsuzawa et al. 2002), and eye–hand coordination (Mushiake, Fujii et al. 1996). Convergent saccades can be produced by low-intensity microstimulation of the SEF (Tehovnik and Lee 1993, Martinez-Trujillo, Medendorp et al. 2004). The SEF has connections with oculomotor centres in the striatum of the BG, SC, and brainstem (Huerta & Kaas, 1990). However, the SEF only makes small contributions to the initiation of gaze shifts, because lesion studies showed that the SEF alone is neither sufficient nor necessary to signal the brainstem saccade generator for saccade initiation. Saccade initiation is entirely absent after a combined bilateral lesion of the FEF and SC, even though the SEF remained intact (Schiller, True et al. 1980, Schiller, Sandell et al. 1987). Also, removal of the SEF does not affect performance in visually guided saccades (Schiller and Chou 1998). Finally, data from a patient with a highly focal lesion of the SEF showed no sign of abnormalities in the execution of anti-saccades, which are internally guided (Husain, Parton et al. 2003).

Neural activity in the SEF appears to be more context-dependent rather than related to saccadic parameters, when compared with FEF neurons (Coe, Tomihara et al. 2002, Amador and Fried 2004, Uchida, Lu et al. 2007). Lastly, the majority of cells in the SEF have activity that is related to error and conflict as well as the anticipation and delivery of reinforcements (Amador, Schlag-Rey et al. 2000, Stuphorn, Taylor et al. 2000) Schall 1997). In addition to reward- and error-related signals similar to those described in the ACC, a distinct population of neurons in the SEF signal conflicts between the movement plan and the outcome. These neurons show elevated activity during a stop signal task in which a monkey is required to cancel the saccade if a stop signal appears, especially during trials when the saccade is stopped successfully. More importantly, the activity was modulated when the movement failed to cancel, because the stop signal was detected past a certain time (Stuphorn, Taylor et al. 2000). The modulation of the response in this population of neurons suggests a conflict between the gaze-shifting and gaze-holding activities in motor areas such as the FEF (Nakamura, Roesch et al. 2005, Stuphorn, Brown et al. 2010). The SEF may therefore play an intermediary role between the motor components of the visuomotor system and the error and reward feedback representations in the ACC, to signal the conflict (Schall, 1997; Schall 2007).

1.4.5.3 FEF

The FEF is considered one of the main visuomotor regions involved in the transformation of visual signals into saccade motor commands (Schall, 1997). In rhesus monkeys, the region is located in the rostral bank of the arcuate sulcus. Neural recordings

of the FEF in visually guided saccade and fixation tasks have shown that roughly half of the neurons have visual responses (Bruce and Goldberg 1985, Schall 1991). More recent evidence suggests that these visual neurons are also involved in active selection of targets for saccades (Schall and Thompson 1999). There are three different pathways by which the FEF exerts control over gaze control: 1) major projections to ipsilateral SC (primarily to intermediate layers) (Leichnetz 1981, Shook and Villablanca 1991)2), 2) topographically organized projections to the caudate of the BG that pass through the striatum and STN, the medial regions of the FEF that project to the central compartment of the caudate and dorsomedial putamen, and the lateral FEF regions that terminate in the caudate and ventromedial parts in the putamen (Shook, Schlag-Rey et al. 1991, Parthasarathy, Schall et al. 1992), and 3) direct projections to mesencephalic and pontine nuclei (Schnyder, Reisine et al. 1985), but more precisely to the interstitial nucleus of the Cajal, medial longitudinal fasciculus, and PPRF. The majority of these projections are to ipsilateral sites, but there are a few contralateral projections as well. The FEF also has major intercortical connections with the SEF and nearly all of the extra-striate visual areas, and weaker connections with the ACC (Schall, Morel et al. 1995).

The FEF is known to be a major contributor in the initiation and control of gaze shifts and microstimulations with a low intensity of evoking saccadic eye movement (Bruce, Goldberg et al. 1985). In addition to single-unit recording data, it shows that a group of neurons in the FEF discharge specifically before and during saccades. Some neurons are also responsive to smooth pursuit eye movements (Bruce, Goldberg et al. 1985, Hanes and Schall 1996). Anatomical studies show that these movement-related

neurons project to the SC (Segraves and Goldberg 1987, Sommer and Wurtz 2000) and neural brainstem saccade generators (Segraves 1992). Another population of neurons in the FEF and SC are active during fixation and exhibit decreased discharges preceding saccades. Robinson and Fuchs (Robinson and Fuchs 1969) were the first to show that the electrically evoked saccades exhibited a quantitative relationship between saccade amplitude and velocity. They also found that the resultant saccade vectors did not vary much based on the initial eye position, but changed with the site of stimulation. Ventrolateral stimulations resulted in smaller amplitude saccades, and as the sites moved to the dorsomedial direction, the saccadic amplitude became progressively larger. A large variety of cells are found in the FEF, including sensory cells that respond to both auditory and visual stimulus, visuo-movement neurons of transient and sustained types, movement neurons, post-saccadic neurons, and other modulators of activity. However, for the purposes of this review, the focus will be on the visual, visuomotor, movement, fixation, and some aspects of the post-saccadic activity of FEF neurons.

The visual responses in the FEF have a latency of 60–120 ms and have topographically organized RF responses that can be phasic (i.e., signalling the presentation) or tonic (i.e., lasting throughout a delay period even after the stimulus is removed) (Mohler, Goldberg et al. 1973, Schall 1991). The duration of discharge is approximately 100 ms for phasic and about 500 ms for tonic responses. Although seldom selective for the shape or features of the stimulus, some visual neurons respond to moving visual stimuli but are not directionally selective. The visual response also shows modulation of activity such as enhancement, suppression (in a similar manner as in the

SC), and prolongation in cases where the saccade is delayed. One of the more distinct modulations of the visual response by visual and sustained visuomotor neurons, which reflects a decisive role of the FEF in the generation of responses, is the change in activity reflecting target selection. In a visual search task with an array of visual stimuli, one appears that has a distinct feature to be distinguished as the target of the saccade. The initial visual response does not discriminate between the target and the distractor being presented in the RF; however, the signal eventually evolves to the target in the RF and not the distractor. In addition, modulation of the visual response suppresses activity corresponding to the location of the RF, where the distractor is located (Schall and Hanes 1993, Thompson, Hanes et al. 1996).

The motor activity of the movement neurons has a latency of 100–200 ms, but it is less for transient visuomotor neurons, and the phasic visuomotor type does not stop responding during the delay. Approximately half of the movement-related neurons have activity prior to unrewarded spontaneous eye movements in the dark, which suggests that FEF movement activity controls purposeful gaze shifts (Bizzi 1968, Bizzi and Schiller 1970). Certain movement neurons discharge specifically before and during the saccades, but usually the offset of activity is on average 35 ms after the offset of the gaze; however, the peak of activity is well aligned with gaze onset in most cases. The movement RFs are larger and more coarsely tuned compared with those in the SC, but there exists a gradual topographical increase in size in the RF when moving from lateral to medial sites in the FEF. Most of the movement activity also shows anticipation related activity based on previous experiences. Because a given neuron fires for a range of amplitudes and

directions other than its preferred gaze vector, the resultant gaze is determined by a population of active cells in the same manner as in the SC (Bruce and Goldberg, 1985 and Schall 1991). A phenomenon uniquely seen in the FEF (amongst cortical visuomotor areas) that illustrates the mechanism of gaze control in the FEF is that saccades are initiated only if activity reach a certain threshold that is unique to each neuron, but this threshold does not vary with changes in saccade reaction time. However, these changes are compensated by differences in the rate of increase in neural activity (Hanes and Schall 1996, Schall 2007). Thus, the motor activity of the FEF resembles an accumulator structure, in which movement is initiated when enough activity is compiled (Schall and Boucher, 2007). A complementary activity to this "rise to threshold" pattern is seen in the fixation neurons of the FEF. If the signal to cancel the saccade is received prior to the motor activity reaching the threshold, the fixation neuron activity begins to rise as the motor activity declines, and vice versa. The winner of the "race" of fixation and motor activities will determine whether a gaze shift will occur (Logan, Cowan et al. 1984, Boucher, Palmeri et al. 2007, Schall and Boucher 2007).

There have been speculations regarding which signals might be carried by the post-saccadic activity of FEF neurons, but here the focus will be on the possibility of a relationship between post-saccadic activity and commands for gaze control. Goldberg and Bruce (Goldberg and Bruce 1990) observed post-saccadic neurons in the FEF, which showed tuning for gaze dimensions and preferred gaze vectors for their discharges. More importantly, they observed that this activity was suppressed whenever a subsequent gaze shift was made, so the signals encoded by this activity were probably not required by the

time the next movement was generated. Goldberg and Bruce also found that many of the visual cells that registered the second motor error also showed a post-saccadic discharge after saccades in the opposite direction of their receptive fields. Based on these results, Goldberg and Bruce suggested that the FEF neurons carried all of the signals needed to successfully perform the double-step saccade task by using a vector subtraction mechanism. The motor error vector of the second saccade was computed by vector subtraction of the dimensions of the first saccade from the retinal error vector of the retinal location of the target. The activity of post-saccadic and visual cells in the FEF was the basis for this computation.

The number and extent of brain areas involved in different aspects of gaze generation (Figure 1.3) and the extensive connection at almost all brain regions (Figure 1.4) indicates the importance of gaze movements in many essential functions and interactions in life.

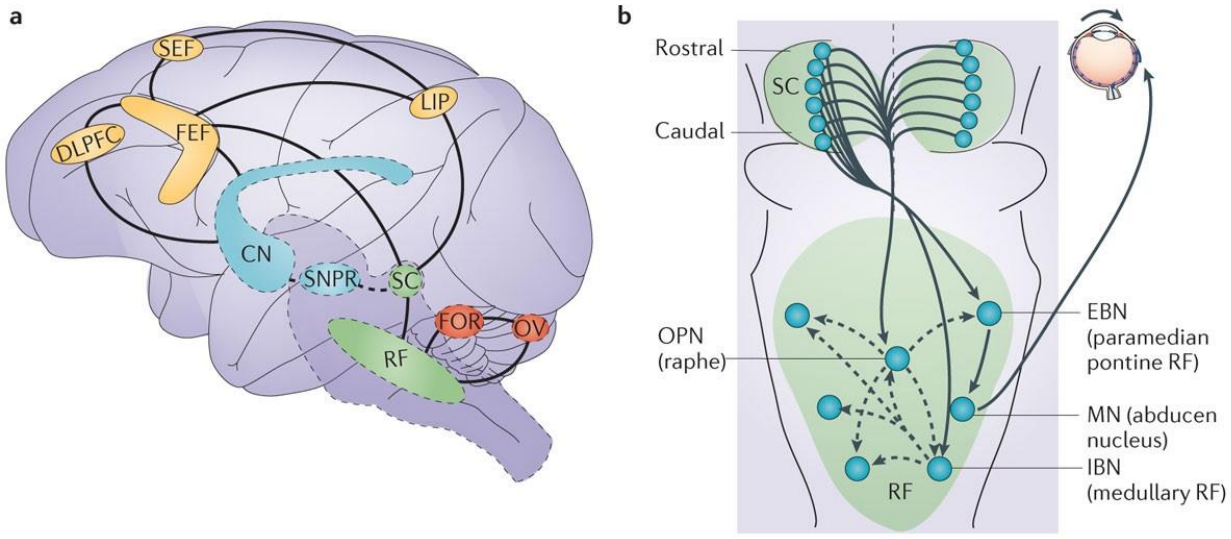

Figure 1.3 The main brain areas that are involved in control of gaze shifts. A) Various cortical and subcortical areas are shown, along with their connections (black curved lines). B) Connection of the superior colliculus with different brainstem nuclei (solid arrows) that control eye movements is shown in this figure, together with interconnections between individual oculomotor nuclei and the brainstem (dashed arrows) (Martinez-Conde, Otero-Millan et al. 2013)

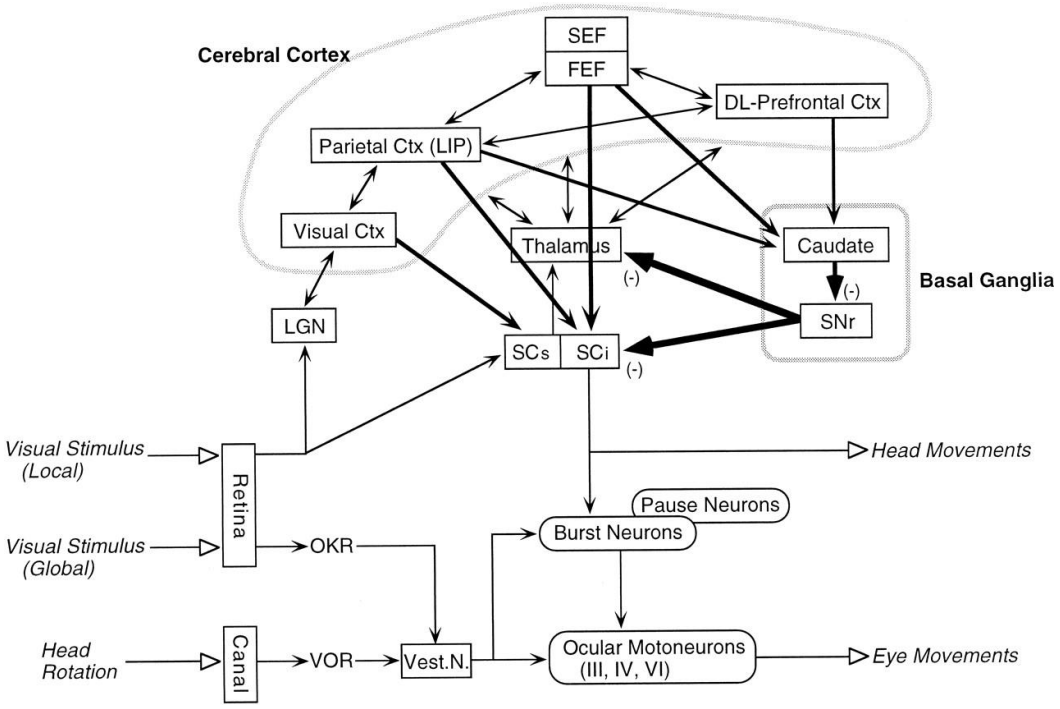

Figure 1.4. Schematic diagram of the connections (i.e., inputs and outputs) between different brain areas involved in the generation and coordination of eye and head movements (Hikosaka, Takikawa et al. 2000).

1.5 Anatomy, Physiology, and Functions of the SC

The SC is central to the circuitry of gaze control. The sensory-motor nature of SC activity, together with extensive efferent/afferent connections with the cortex, thalamus, BG, and brainstem saccade generators, makes the SC a key region in gaze generation (Goldberg and Wurtz 1972, Goldberg and Wurtz 1972, Sparks 1978, Wurtz and Albano 1980, Sparks and Porter 1983,

Sparks 1989, Sparks and Hartwich-Young 1989). This structure lies in the dorsal part of the midbrain and contains seven anatomically distinct, alternating grey and white layers, which are functionally divided into three compartments. The superficial layers consist of the stratum zonale, stratum griseum superficiale, and stratum opticum. This layer mainly contains neurons with activities related to the presence of visual stimuli. The first two layers receive direct input from the retina and the striate cortex, and the last layer receives input from the frontal lobe. The intermediate layers involve the stratum griseum and album intermediale, which contain neurons responsive to sensory stimuli from the different modalities of vision, auditory, and somatosensory stimuli. Most of the neurons in this area have a biphasic response; the initial response is related to the sensory stimuli and the latter is related to movement. The deep layers involve the stratum griseum and album profundum. The majority of neurons in this area have only movement-related activities, which project to the brainstem saccade generators. This division is based upon behavioural, anatomical, and electrophysiological studies (Wurtz and Albano 1980, Sparks 1988). However, there is controversy concerning whether these layers are functionally connected. Edward (1980) used anatomical methods and morphological, connectivity, and receptive field properties to suggest that these layers are functionally distinct. In contrast, inactivation provided evidence for independent activities in each region (Sparks 1999). However, there have been many anatomical and electrophysiological studies that suggested inter-laminar connections between the SC layers (Grantyn, Shapovalov et al. 1984, Moschovakis, Karabelas et al. 1988, Isa, Endo et al. 1998, Doubell, Skaliora et al. 2003).

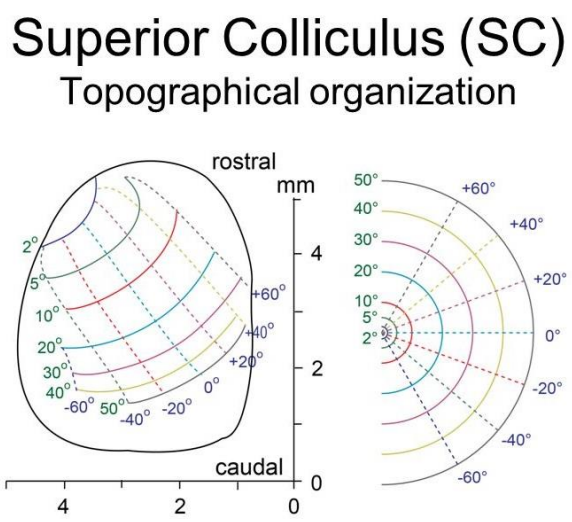

Figure 1.5. Topographical organization of the superior colliculus (SC). The anatomical location of neurons in the SC correlates with the response field location in the visual field for visual neurons, and with the direction and amplitude of gaze generated by the motor neurons in that location (Gandhi and Katnani 2011).

1.5.1 The superficial layers

The cells located in these layers show a robust peak of activity following the appearance of visual stimuli in their receptive fields. The latency of the visual response in this region ranges from 40–60 ms, which decreases with increasing size of the visual stimulus(Goldberg and Wurtz 1972). Most of these visual cells show strong habituation effects in response to repeated presentations of stimuli, with the exception of approximately 10% of the cells that show directional selectivity in their responses to moving stimuli and modulations related to the stimulus shapes. The remaining cells are not directionally selective, and none are selective for the velocity of movement. In addition, these cells do not show modulation in their activity in response to shape, contrast, or orientation of stimuli (Schiller and Koerner 1971, Cynader and Berman 1972, Goldberg and Wurtz 1972). The visual neurons in the superficial layers are divided into two groups based on the presence or absence of enhancement and/or suppression of their

responses (Goldberg and Wurtz 1972b). These effects are seen in some of the more ventrally located visual neurons. The enhancement effect is manifested by an increase in firing rate when the stimulus is to be the target of the saccade, and the suppression decreases in the visual response during the initiation of the command to move the eyes. Because of the similarities between these responses with the FEF visual response, it has been suggested that these modulated SC visual cells receive their input from the FEF, whereas the more dorsal neurons that lack such modulations receive inputs from the retina and striate cortex. The extent of inputs received from the striate cortex varies in different organisms, and its importance has been questioned because of the high number of dissimilarities in visual response properties and receptive field organizations in the two regions (Sparks and Hartwich-Young 1989). However, in phylogenetically newer mammals, it is relatively more extensive, because of an accelerated increase in the size of the cortex (Wurtz and Albano 1980). Nevertheless, Schiller and colleagues (Schiller, True et al. 1979) reported that ablation of the monkey's V1 did not render the animal completely blind, and the saccades to visual targets were still intact. However, after simultaneous V1 and SC ablation, the animals suffered from complete loss of the visual field related to the ablated regions.

The visual responses of these neurons are organized as RFs, which refer to the area where the presentation of the visual stimulus produces a maximal response. The centre of the RF is where the stimulation produces a maximum response, and as the stimulation moves away from this location, the response attenuates and will diminish at some point, depending on the size of the receptive field (Goldberg and Wurtz 1972, Goldberg and Wurtz 1972, Wurtz and Albano 1980). The RFs are topographically organized, and all cells have contralateral RFs, with the

exception of some cells with RFs at the vertical meridian that contain some overlapping areas from the ipsilateral visual field. The foveal vision is overrepresented in the SC, with the central 10° represented by over 30% of the SC spaces that are represented rostrally, while more ventral cells have more lateral RFs. The cells in the medial SC have upper visual field representations, and the lateral SC represents the inferior field. Moreover, more dorsal cells have close and small RFs. By moving ventrally in the superficial layers, the RFs get larger and have less defined boundaries (Figure 5) (Cynader and Berman 1970, Goldberg and Wurtz 1972a).

1.5.2 The Intermediate layers

These layers contain a much more diverse set of neurons, not only because most cells have a movement and cognitive related activity, but also because many cells are responsive to auditory and somatosensory stimulation (White and Munoz, 2010). To briefly review, the cells that respond to sensory stimuli in the SC are mostly multimodal, but the tuning for the stimulus localization is less defined compare to the visual RFs of the same cells. In addition, the maps of RFs for auditory and somatosensory stimuli are topographically organized (Figure 5) but in different frames of reference; the former RF is encoded in a head-centred frame of reference (although it is modulated by changes in gaze position) (Groh, Trause et al. 2001), and the latter is encoded in a body-centred frame of reference. Lastly, the latency of responses to both are shorter and more transient than the visual response, and in multimodal cells the sensory related response can be modulated by presenting more than one stimulus at once, or by changing their gains (Sparks 1986, Jay and Sparks 1987, Jay and Sparks 1987). The most important types of

neurons in intermediate layers are visuomotor neurons; as the name implies, they respond both to the appearance of visual stimuli and to the initiation of gaze shifts.

Before describing these cells and their response, there are two important issues that need to be discussed. The first issue is a comparison between the nature of visual signals in the intermediate and superficial layers, and the second concerns the characteristics of motor related signals and their corresponding RFs:

1) The most noticeable differences between the visual responses compared to the superficial layers is that some visual responses are not transient, and show a high frequency burst followed by a sustained lower frequency response, which could be related to the processing of cognitive aspects, such as target selection or for movement preparation (McPeek and Keller 2002). Interestingly, White et al. (White, Boehnke et al. 2009) reported that this type of neuron is very responsive to differences in luminance of colour stimuli. This might suggest that unlike superficial visual neurons, intermediate sustained-type neurons receive input from both the broadband and colour opponent regions of the geniculostriate pathway. Because differentiating the stimulus of interest from many other possibilities in the environment should occur prior for a saccade initiation command, the visual neurons in the superficial SC have higher modulations in response to salience. The evidence for this comes from experiments that suggest the superficial SC receives direct input from visual cortical areas V1, V2, V3, and MT (Fries 1984), and that these neurons respond to changes in a broader aspect of stimulus characteristics compared to the top intermediate visual responses (Fecteau and Munoz 2006).

2) There are different types of motor activities related to movement of gaze (Robinson 1972, Sparks 1975, Freedman and Sparks 1997), head (Walton, Bechara et al. 2007), shoulder, pinnae (Cowie and Robinson, 1994), whiskers (Hemlet and Keller 2008), and reach (Werner 1993) in the intermediate and deep layers of the SC. The nature of all movements is to orient the body, including the gaze, toward the stimulus of interest in the environment. In addition the SC neurons are active prior to vergence and smooth pursuit type gazes shift, however, stimulation of the SC does not evoke such movements (Schiller and Koerner, 1971; (Wurtz and Goldberg 1971). Because the focus here is on the saccadic gaze shift components of orienting movement, this discussion refers solely to this type of gaze movement unless otherwise noted. The latency of motor responses varies greatly, depending on the neuron type and the type of gaze shift (e.g., visually versus memory-guided gaze shifts), and the onset of activity varies from 180 to 20 ms prior to the start of gaze shifts. The timing of the peak of activity also differs depending on the neuron and task types, but it is usually within 30 ms of onset of gaze and is often aligned with gaze (Mays and Sparks 1980, Sparks and Hartwich-Young 1989, Munoz and Wurtz 1995, Munoz and Wurtz 1995). The RF of movement-related neurons is the direction and amplitude for which the neuron fires maximally, and it is therefore important to note that the motor RFs are more coarsely tuned compared to the visual RFs. There are also neurons that have open RFs that fire for any amplitude greater than their preferred saccade vector. The movement activity RF is also topographically organized, and it is very closely aligned with the visual RF, so that the rostral areas are active for small amplitude saccades, and more ventral movement activities are related

to larger amplitude saccades. The neurons in the medial SC code for upward movements and the lateral SC code for downward movements. The majority of RFs represent the contralateral field, but there is some degree of overlap to the ipsilateral field, more so than those seen in the visual RF, especially in neurons with RFs close to the vertical meridian. Moreover, the size of the RF also changes with the anatomical location of the neurons, with rostral more superficial neurons having smaller and closed receptive fields, and by moving deeper and more ventrally neurons with larger motor RFs, and some with open motor RFs, are encountered (Robinson 1972, Sparks, Holland et al. 1976, Marino, Rodgers et al. 2008). The smaller amplitude saccades are also overrepresented in the SC, with more than 70% of the SC space coding for saccades with amplitudes of 10° or less. In cases where both vision and movement coexist and are related, the RFs of each are usually aligned spatially but are not necessarily of the same size (i.e., those having a closed visual RF, but an open movement RF) (Mohler and Wurtz 1976, Munoz and Wurtz 1995). Because a given motor neuron is active for a relatively broad range of saccadic amplitudes and directions, a population of motor neurons are active for a given saccade (approximately 28% of motor neurons); therefore, saccade metrics are defined by this population of activity. The location of the active population determines the saccade direction, and the centre of that active population encodes the desired amplitude of the saccade (Lee, Rohrer et al. 1988, Gandhi and Katnani 2011). Moreover, based on observations of the higher discharge of SC neurons in visually compared with memory-guided gaze shifts, the relatively lower velocity of the latter as previously described (Gnadt, Bracewell et al. 1991, Sadeh, Sajad et al. 2015, Sadeh,

Sajad et al. 2018), and that increases in frequency of stimulation are related to an increase in saccade velocity following (Stanford, Freedman et al. 1996), it has been proposed that the activity in the SC also encodes the saccadic velocity.

There are five important types of visuomotor neurons that are found in the intermediate layers as listed and explained here, by the order of their depth (dorsal to ventral) in the SC:

1. Visually triggered movement neurons (VTM): These neurons were first characterized by Mohler and Wurtz (Mohler and Wurtz 1976); they discharge before saccades into their RF, but only to a visual target in the RF. Spontaneous eye movements without a visual target or goal do not cause a discharge in these cells. These VTM are located at the dorsal border of the stratum superficial and intermediate layers, and their firing patterns are very similar to the burst type movement neurons. Their visual response is not considered as a "gating" mechanism for deeper movement activities because the movement part of the neurons and the movement-related activity can be triggered without a visual response (Wurtz and Albano 1980).

2. Quasi-visual neurons (QV): These neurons were described by Mays and Sparks (Sparks and Mays 1990), and have a constant latency visual response, with a sustained following activity until a saccade of appropriate amplitude and direction occurs. The QV cells continue to discharge even after the target is extinguished. Furthermore, they increase their firing rate with increases in current and desired eye positions, and this suggests that the QV cells are carrying information regarding the desired eye displacement. Because these cells begin their discharge long before the onset of a saccade and do not

discharge discrete bursts of activity related to gaze onset, and because the offset of activity is not well aligned with gaze offset, these QV cells are thought to be the relay points that transfer the visual signal and the related motor and retinal error information from superficial to deep layers (Wurtz and Optican 1994, Sparks 1999).

3. Visuomotor neuron-burst type neurons: These cells were characterized and categorized as a distinct category by Munoz and Wurtz (1995a and 1995b), and have a relatively weaker visual burst followed by a stronger transient burst of activity related to the onset of saccade, with almost zero firing during the period between the stimulus presentation and saccade onset. The latency of motor burst varies between 40–100 ms, and the peak is well aligned with the gaze onset and is shut off at the time when the eye reaches the target. The majority of both the visual and motor RFs of these cells are closed and relatively smaller. This group of visuomotor cells is more homogenous compare to the build-up type.

4. Visuomotor build-up type neurons: Although these types of neurons were previously categorized as LLBN (Mays and Sparks 1980 and Wurtz and Albano 1980), a later study by Munoz and Wurtz (1995 a, 1995b) led to new findings that changed the labelling category. First, by using a memory-guided saccade, they showed that there is a slow rise in motor activity, which followed a burst of action potentials in response to the stimulus presentation. This visual burst is relatively stronger, and it is almost equal to the motor burst that followed. The slow rise starts as early as 200 ms prior to gaze onset, increases, and reaches its peak around the time of gaze onset. Unlike the burst type, the peak is not very well aligned with onset of the gaze, and also is not shut off after the gaze offset,

and continues firing for approximately 30 ms afterwards. The alignment of the peak and its decay in build-up depends on the saccade vector. From the saccades to the centre of the RF, the peak is well aligned with saccade onset and the decay occurs fast. But for larger amplitudes, the peak occurs later than the gaze onset and decays more slowly. Most of the movement RFs of these cells are open, and those with closed RFs have larger movements compared to the burst visuomotor cells. The activity in the population of build-up cells resembles those seen in the "moving hill" of activity in a cat SC during head unrestrained gaze shifts (Munoz, Guitton et al. 1991). These cells are active for a large range of saccades, and those with open RFs start their activity sooner, such that the gaze shifts are larger than their preferred amplitude. Therefore, more caudal cells are activated earlier, and more rostral cells are activated later until the centre of activity becomes the cells with the preferred amplitude identical to that of the planned saccade (Munoz ad Wurtz 1995b).

5. Fixation neurons: These neurons were found both in cats (Munoz and Guitton 1991) and monkeys (Munoz and Wurtz 1993). They are tonically active during fixations, decrease in discharge at the onset of saccades, and are silent during the saccades. Fixation neurons are found in the rostral pole of the SC. Munoz and Wurtz (1995a) suggested that these cells are the destination for the "moving hill" because the moving hill stopped at this region, the activity is related to fixation, and the cells show a build-up burst for very small saccades (less than 5°), similar to the build-up observed with visuomotor cells. More recently, these cells have been linked to the generation of micro-saccades, which are essential for the prevention of fading of the visual image due

to habituations, and have also been linked to spatial attention (Hafed 2011, Hafed and Krauzlis 2012).

1.5.3 The deep layers:

Neurons in the deepest layers of the SC are almost completely silent in response to visual stimulation, and display a very vigorous (250 spikes/second) and short latency (20–50 ms) burst of activity prior to the onset of the gaze. The movement RFs are well-defined and the majority are closed (Mays and Sparks, 1980). In the head unrestrained experiments of Freedman and Sparks (1997), the activity of the deep layer burst neurons was best correlated with gaze movement compared to eye or head movements alone, therefore, it was suggested that these neurons provide the gaze displacement command to the brainstem, which then progressed to separate pathways for eye and neck muscle control. More recently, Walton et al. (2007) found neurons in deep layers of the SC with modulations to head only movements. The gaze-related neurons were almost silent during these head only movements. The majority of these "head" cells show an increase in activity; however, some decrease or even paus their activity during their movements. There was no consistent topographical organization for these neurons, without any defined RF or directional tuning. The authors ruled out the possibility of these cells carrying the vestibular signal based on two observations: 1) the cells in the sample have a predictive firing, which started prior to the onset of head movements, and 2) passive whole-body rotations did not cause a response in these cells. Furthermore, the authors suggested that a possible role of these head cells is controlling head movements, which are independent of gaze shifts, and they could

therefore be carrying a corollary discharge for changes in the eye in head position(Freedman 2008).

1.5.4 Cognitive issues influencing the SC activity

Several cognitive factors have been shown to influence different aspects of eye movements, such as the probability of occurrence, latency, accuracy, and speed of saccadic eye movements (Kowler 1990). Almost all of these processes are likely to impact the discharge of the SC neurons involved in controlling gaze shifts. The most established cognitive states, which influence the SC activity, include the patterns of the SC neurons ascribed to a number of cognitive states, including spatial attention (Goldberg and Wurtz 1972, Kustov and Robinson 1996), working memory (Mays and Sparks 1980), selection of response (Glimcher and Sparks 1992), saccade preparation (Dorris, Pare et al. 1997), target selection (Basso and Wurtz 1998, Horwitz and Newsome 1999), and updating the target of future saccades (Dash, Yan et al. 2015). In addition, during most behavioural circumstances, several cognitive factors might have an immediate impact, and therefore, the SC activity would be affected by all of these factors. Hence, the effects seen in the SC neural discharge might not be due to a single cognitive factor. Moreover, even if the variable of interest is carefully controlled, it is quite likely that it would affect more than one area of the brain, which potentially could affect the SC neurons differently, and therefore, lead to misinterpretation of causal roles. Finally, another problem in most experiments is that the activity of neurons was examined under conditions in which one cognitive factor under investigation was assumed to be constant, and only the evoked or non-evoked responses were

considered, while modulation of neural activity might have occurred and been easily missed (Sparks, 1999).

1.6 Spatial Models Proposed for Coding of Gaze

The main focus of my dissertation was to investigate the spatial information encoded by the visual and movement activity of the SC neurons, and to determine how the spatial information evolves within and between the neural activities. For the purpose of gaze movements, it is important for the neural network to not only identify the visual target location, but also to determine the frame of reference for encoding the information. Frame of reference refers to the rigid body that the other locations are defined in relation to (Soechting and Flanders 1992). For example, when looking at a painting on the wall, if the defined frame of reference is the wall itself, then the location is constant regardless of movement of body parts. However, if the frame of reference of the painting is defined relative to eye location, the encoded spatial location changes as the eyes move, despite the painting being physically motionless. This is essential for accurate and consistent representation of spatial information for gaze movement because the eyes, head, and even the body routinely move in orientational movements to different stimuli. Moreover, because the spatial information can change from the input (visual) to output (motor) levels, it is possible that the frame of reference also shifts through this visual to movement transformation (Soechting and Flanders 1992, Soechting and Flanders 1992, Optican 1995, Snyder 2000). In addition, gaze can be in response to other sensory modalities (i.e., somatosensory or auditory) (Groh and Sparks 1992, Groh and Sparks 1996, Maier and Groh 2009) that are encoded in different frames of reference. In addition, when several sensory modalities

merge, for example, when a stimulus has both auditory and visual information, it is necessary for the frames of reference to be able to be integrated and interconverted to produce an accurate net result of the spatial information regarding that stimulus, and consequently provide a successful gaze shift toward it (Crawford, 1994; Wallace et al., 1998; Mullette-Gillman et al., 2005). Spatial information can be further described in relation to self (egocentric) or to external objects (alocentric). In the gaze movement, the eyes, head, and body move in relation to each other, and thus, the egocentric representations are described in the coordinate systems relative to these effector components as eye, head, and body centred (Olson and Gettner, 1995; Chen et al., 2014; Ekstrom et al., 2014; (Keith, DeSouza et al. 2009, DeSouza, Keith et al. 2011, Sajad, Sadeh et al. 2015). In a natural setting, when there are many visual stimuli present in the visual field, allocentric representations have influence. But in the current dissertation, the experiments involved a single visual target, and therefore, the focus here is on egocentric representations (Li, Sajad et al. 2017).

Most experiments regarding the egocentric frame of reference were done in head-restrained experiments, and the collective evidence suggested that a predominant eye-centred representation in most brain areas involved in gaze movement such as LIP, FEF, SEF, and SC (Bruce and Goldberg 1985, Russo and Bruce 2000, Cohen and Andersen 2002, Medendorp, Goltz et al. 2003, DeSouza, Keith et al. 2011). However, a fixed eye-centred representation is not sufficient for eye movements because the retinal image is essentially unstable as a result of rapid changes in eye movement during the gaze shift. Hence, a remapping mechanism has been proposed to represent the future (i.e., post-saccadic) spatial information, and has been characterized in various brain areas and for other movement systems (Duhamel, Colby et al.

1992, Henriques, Klier et al. 1998, Medendorp 2011). Another caveat of a fixed, eye-centred representation is the vision to action transformation, which requires changes in representation, because the components of each are moving in relation to one another, and the coordinate systems of the effectors are also different. One of the proposed mechanisms for integrating the information regarding the relative position of each effector system is the gain field phenomenon, which is represented by the modulation in neural activity dependent on the relative location of one effector system to another. Gain fields were first characterized by Andersen and colleagues as variations in neural responses to a visual stimulus on a fixed location on the retina, depending on the changes of eye position in the orbit (i.e., eye position-dependent modulation), and this has been since observed in several other visuomotor brain areas (Andersen 1985, Andersen, Essick et al. 1985, Snyder, Grieve et al. 1998, Dash, Yan et al. 2015). The gain field effect was also proposed to be a central mechanism employed by the brain to transform the representations between effectors, and also to interpret a given location based on population activity, which utilizes multiple frames of reference (Pouget and Sejnowski 1997, Pouget and Snyder 2000). Despite the dominance of eye-centred coordinate systems in the visuomotor brain areas, a few brain areas have been shown to have head- and even space-centred (i.e., allocentric) frames of reference; yet, even these areas exhibited gain field modulations in activity (Snyder et al., 1998; Brotchie et al., 1995; Galletti et al., 1995; Duhamel et al., 1997; Fogassi et al., 1992). Frames of reference are not necessarily fixed to one specific representation, and in addition to transformation, they can be an intermediate between two cardinal reference frames. For example, auditory RFs have been shown to be encoded in intermediate reference frames in between the eye- and head-centred frame of reference (Jay and Sparks 1984, Groh and Sparks

1992), which also occurs in other gaze areas and other motor systems (Avillac, Deneve et al. 2005, Pesaran, Nelson et al. 2006, Mullette-Gillman, Cohen et al. 2009, Bremner and Andersen 2014). Further evidence regarding the frame of reference and coordinate systems, which are utilized for encoding spatial information, comes from micro-stimulation studies that employed electrical micro-currents delivered to different gaze areas to study the resultant eye and head movements. In experiments where the heads of the subjects were fixed, the micro-stimulation of several cortical and subcortical areas evoked eye movements with fixed movement vectors that were centred at the initial fixation points (Bruce and Goldberg 1985, Tehovnik and Lee 1993, Robinson and Kertzman 1995). Head unrestrained experiments allow for dissociation of head-/body-centred representations, space-centred representations, and even the possibility of intermediate reference frames. To address these questions in a group of experiments, it was found that microstimulations in the LIP, FEF, and SEF areas, which in a head-fixed setting showed fixation-centred coordinates, actually yield hybrid reference frames between the eye and head representations (Martinez-Trujillo, Medendorp et al. 2004, Constantin, Wang et al. 2007, Monteon, Wang et al. 2013). As suggested by these studies and the studies discussed earlier, it is possible that different coordinate systems exist at various brain areas, even within the same areas, and different coordinate systems could be utilized depending on the context and movement vector (Crawford, Henriques et al. 2011, Monteon, Avillac et al. 2012).

Although many studies have shown that both sensory and movement-related neural signals exist in the gaze areas of the brain, most studies concerning the spatial coding of gaze movements examined the combined sensory and motor activity, or studied them in separate experiments. Because of the previously mentioned implications regarding how and where the

sensory signals are transformed into signals for gaze movement, simultaneous analyses of these signals and their relationships to one another may provide valuable information on the roles of individual gaze areas, as well as their relationships to one another. In addition to the difficulties in separating these signals into individual components, the challenge also exists regarding the utilization of behavioural errors to dissociate between sensory and movement signals (Flanders, DerSimonian et al. 1992, Platt and Glimcher 1998, Vesia, Bolton et al. 2013). However, this is not as reliable in neurophysiological studies because of the reliance on average firing rates and positional data (Snyder 2000). Hence, to effectively achieve the separation between sensory and movement signals, temporal dissociation between the two events and spatial separation between sensory stimuli and gaze direction are often employed (Funahashi, Chafee et al. 1993, Gottlieb and Goldberg 1999, Sato and Schall 2001, Munoz and Everling 2004). The general consensus of these studies, which attempted to separate the visual and motor components of gaze activity, was that the visual related signals encode the stimulus direction and the movement encodes the gaze direction (Sato and Schall 2001, Munoz and Everling 2004). However, the generalizability of these findings was limited by the special circumstances and the cognitive demands that were present during these studies, which could have modulated the neural correlates of the spatial information (Sato and Schall 2001, Fernandez-Ruiz, Goltz et al. 2007, Johnston, DeSouza et al. 2009, Hawkins, Sayegh et al. 2013). Thus, the observed transformation in these studies could be due to the cognitive to motor function transformation, rather than to a visual to motor transformation, which occurs during a standard visual saccade. It is also possible that the motor activity encodes the individual effector movements, and that the final desired position, rather than solely a displacement vector, is not addressed in a head-restrained setting.

Nevertheless, most neurophysiological studies found that neural activity best correlated with a gaze displacement vector rather than the eye and head vectors, individually (Guitton, Munoz et al. 1990, Freedman and Sparks 1997, DeSouza, Keith et al. 2011), and similarly microstimulations of different gaze areas evoked natural coordinated eye and head movements (Harris 1980, Guitton, Munoz et al. 1990, Klier, Wang et al. 2003, Martinez-Trujillo, Medendorp et al. 2004, Knight and Fuchs 2007). Interestingly, the latter observations were entirely at levels upstream of reticular formation nuclei, and studies in the areas downstream showed that microstimulations of the gaze structures at this level evoke not only individual eye and head movements, but also movements along specific axes (Klier, Henriques et al. 2002, Sparks 2002, Klier and Crawford 2003, Klier, Wang et al. 2003, Farshadmanesh, Klier et al. 2007). Nevertheless, from the prior discussions of the coordinated eye and head movements, it is not completely clear when and how the signals for independent eye and head movements dissociate because some micro-stimulation and neurophysiological studies suggested that signals for head movements also exist at the level of the cortex and SC (Chen and Walton 2005, Chen 2006, Stuphorn 2007, Walton, Bechara et al. 2007).

Based on the above, there are several important questions that need to be clarified to better understand how the spatial information is encoded and used for the generation of gaze movements to visual stimuli. 1) It is not clear how the signals related to visual stimuli are transformed to gaze movement commands. 2) In what frame of reference are these signals (i.e., visual and gaze movement) encoded, and is there a reference frame transformation? 3) Because the various studies suggested different levels and brain areas for these transformations, where do these transformations occur? 4) It is also essential to address what specific spatial information

is being encoded by each of the visual and movement signals (i.e., the stimulus location versus gaze displacement vector). 5) Are the signals related to a specific effector and is there a position based (i.e., gain) modulation?

1.7 History and Summary of the Model-Fitting Methods Used in the Current Thesis Project

To address the questions raised in the previous section, it is important to develop a strategy to approach them simultaneously, assess how information is integrated by the brain areas, and create an experimental setting that more closely mimics the natural behaviour. Most previous studies that aimed to determine the frames of reference of different sensory modalities were performed in a head-restrained setting, and thus did not differentiate between head- and space-centred frames of reference (Stricanne, Andersen et al. 1996, Avillac, Deneve et al. 2005, Porter, Metzger et al. 2006). In addition, the limitations of these studies included uses of fixed spatial locations of the stimuli, lack of natural coordinated eye and head movements, and limitation of the study to two-dimensional components of movement. Determining the frame of reference and what spatial information is being encoded in that coordinate system is closely linked to the concept of the RF, a region of space in which the presence of a stimulus or movement toward that location changes the firing rate activity of the neuron (Hubel and Wiesel 1959, Wurtz 1969). Therefore, mapping and studying the RF of the neurons provide insights to both the frame of reference, the spatial information being encoded by individual neurons, and the population of the neurons. Keith et al. (Keith, DeSouza et al. 2009) developed a method for determining spatial information and the frames of reference of neurons that is based on finding the most coherent activity (i.e., less variability across trials in spatial positions averaged across all

positions) and treating the spatial positions as continuous variable, which is more applicable to natural eye and head movements. Because different combinations of eye and head orientations are possible in natural gaze movements, treating gaze positions as discrete and fixed entities does not reflect the natural settings, and only considers limited possibilities (Glenn and Vilis 1992, Keith, DeSouza et al. 2009). In addition, this method takes into account the torsional components and variabilities, which are essentially absent in head-restrained settings, but have significant contributions to larger coordinated eye and head movements. The details of this method are discussed in the subsequent sections of this dissertation, but the fundamental approach is based on non-parametric regression analyses of the neural activity, and determining the quality of the fits in various frames of reference-spatial information combinations (i.e., head- and space-centred frames of reference, and target and final gaze position spatial information) by obtaining the predictive sum of squares (PRESS) values; the smaller the PRESS for a given reference frame candidate, the more coherent, and thus the better the fit of that candidate (Keith, DeSouza et al. 2009). This method was used in recording the neural activity of the SC neurons by DeSouza et al. (DeSouza, Keith et al. 2011) in reactive saccade tasks and in visuomotor activity. The frame of reference of the SC neurons was found to be in the eye coordinates, and the combined activity of all neurons recorded preferably encoded the saccade target location in the eye frame of reference. Although the head- and space-centred frames of reference were significantly excluded in this study, the final gaze position as a spatial coding scheme was not significantly ruled out. In addition, this study showed that eye dependent gain field modulations exists in the SC neurons, however, when these modulations where excluded from the analyses, the overall results remained unchanged (DeSouza, Keith et al. 2011).

1.8 Goals and Hypotheses of the Current Thesis

Despite the evidence and studies that were done thus far to investigate the spatial information encoded by the neurons in different gaze areas and how and where this information is transformed into signals for gaze movements, some important aspects remain unclear. This dissertation aimed to provide evidence to clarify some of these points. We recorded the activity of the SC neurons during head unrestrained gaze shifts in different behavioural settings (memory delay and reactive tasks), and applied an extended version of the methods of Keith et al. (Keith, DeSouza et al. 2009), as well as further additions and new approaches, in order to study the spatial information, frames of reference, the visual to motor transformations, and possible task-dependent changes of these processes. First, we are interested in determining the spatial information and the frames of reference that are encoded by neural activity of different types of SC neurons. As discussed previously, the various studies that were done previously had some limitations, such as the head-fixed settings, using micro-stimulation, fixed and limited spatial locations, and using cognitive demanding tasks that may have altered the RF of the neurons. DeSouza et al. (DeSouza, Keith et al. 2011) addressed several of these limitations; however, in this study, different types of neurons and activities were not clearly dissociated from one another, and only the combined activity was considered and analyzed. We used a memory delay paradigm to distinguish between visual and movement-related activity in the SC neurons, to categorize them into different neuronal types and analysed them separately to compare and contrast the spatial information and the frames of reference being encoded by these activities. Furthermore, this allowed us to determine if there was a visual to motor transformation between, or even within, the individual neurons in the SC. In addition, we added to our analyses

the possibility of neurons encoding the effector specific movements, such as eye in head location or head in space position, and also the possibility that neurons encoded the displacement vectors rather than final positions, thus allowing us to differentiate between coding for the saccadic goal versus displacement vectors (Sparks 1989, Stanford and Sparks 1994, Bremmer, Kaminiarz et al. 2016). Based on the previous studies and our current understanding of the gaze system, we hypothesize that the predominant frame of reference in the SC neurons remains in the eye-centred frame of reference regardless of activity and neuron types. In addition, given the different outputs/inputs from various layers of the SC (Moschovakis, Karabelas et al. 1988, Moschovakis, Karabelas et al. 1988, Sparks and Hartwich-Young 1989, Schlag-Rey, Schlag et al. 1992, Sommer and Wurtz 2004), and the functional organization of the SC in a layered structure, we hypothesize that the different layers of the SC (and therefore different neuron and activity types) encode different spatial information that is related more closely to input information (i.e., target location) in visual activity layers, and more closely related to gaze movement during the motor activity. In addition, we introduced and utilized the idea of intermediate spatial codes, similar to the intermediate frame of reference that was discussed previously, and thus, we were able to characterize the spatial code of different neural activities as being more closely related to target coding versus gaze coding, and consequently provide further evidence for visual to motor transformation between and within the SC neurons. We also investigated the spatial information and frame of reference of the neural activity in the reactive saccade task for the same neurons, which were investigated in the memory delay task. This allowed us to investigate if the spatial information and reference frames changed depending on the demands of the task (i.e., the working memory process in the memory delay paradigm), and induced saccadic errors

which may have shifted the spatial codes (Miller, Erickson et al. 1996, Ohbayashi, Ohki et al. 2003, Bays, Gorgoraptis et al. 2011, Hollingworth 2015, Sajad, Sadeh et al. 2016) (Figure 1.5). We also used step-by-step analyses of smaller time windows of the neural activity during the reactive task to investigate if there was a change in spatial code, and subsequently, a visual to motor transformation in this task similar to what was reported in FEF neurons during the memory delay task (Sajad, Sadeh et al. 2016). My hypothesis is that a visual to movement transformation will still exist in the eye frame of reference, but the transformation may be to a lesser extent than what is expected in the memory delay task because of possible errors and noise induced by the working memory, and to other cognitive processes that have a higher demand on the memory delay task (Fig 1.5).

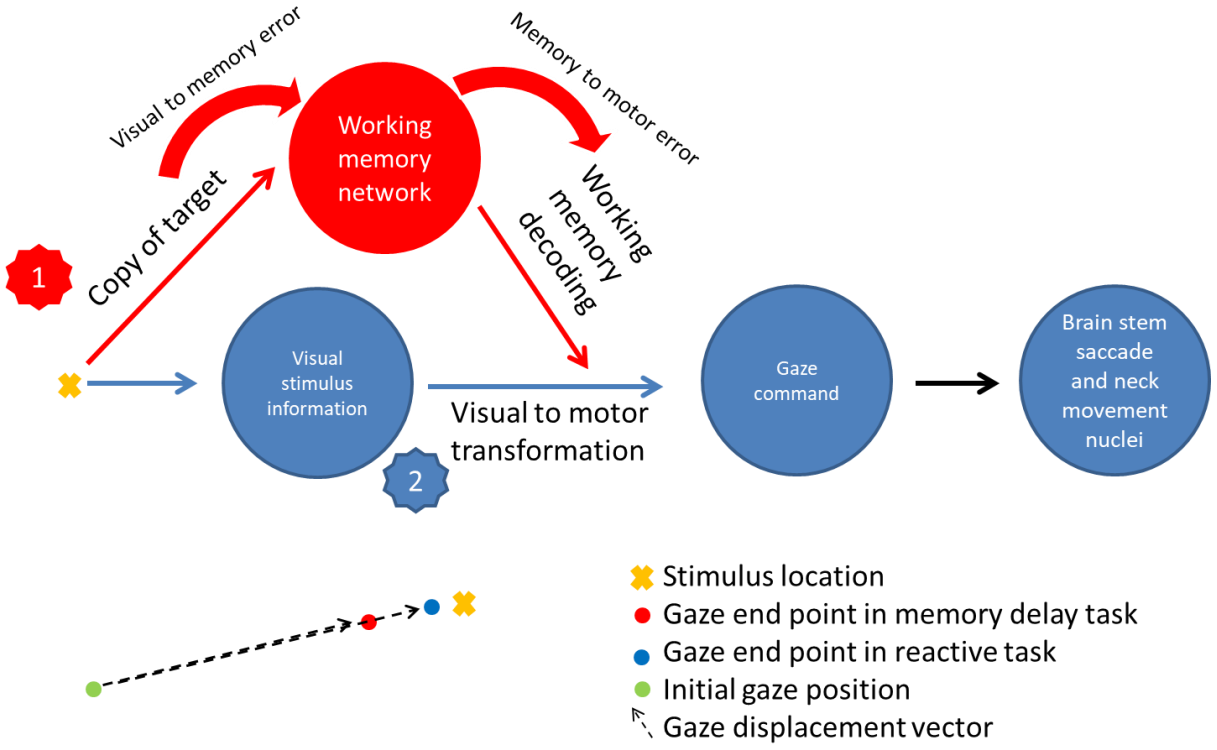

Figure 1.6. Schematic diagram of networks involved in saccade generation for hypothetical gaze shift in memory delay (pathway 1) and reactive tasks (pathway 2) (Bottom left). Flow of signals from one network to another is indicated by blue arrows for a reactive task, red arrows for a memory delay task, and black arrows for the final common path. In pathway 1, the input from the retina concerning the stimulus is sent to the working memory network, which retains the information for a quick retrieval, and to use the stored information rather than actual position of the target for generating gaze commands. This additional "noise" may contribute to gaze end point inaccuracies, which is shown in the schematic of a gaze shift to the visual target (orange cross), for which the difference between the actual location of the target and the gaze end point (red circle) is greater than the difference between the gaze end point in a reactive task (blue circle) because of the more accurate target spatial information, and a more accurate gaze command (pathway 2).

Chapter 2

Spatial transformations between superior colliculus visual and motor responses during head-unrestrained gaze shifts

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2.1 Abstract

We previously reported that visuomotor activity in the superior colliculus (SC) –a key midbrain structure for generation of rapid eye movements— preferentially encodes target position relative to the eye (Te) during low-latency head-unrestrained gaze shifts (DeSouza et al. 2011). Here, we trained two monkeys to perform head-unrestrained gaze shifts after a variable post-stimulus delay (400-700ms), to test if temporally separated SC visual and motor responses show different spatial codes. Target positions, final gaze positions, and various frames of reference (eye, head, and space) were dissociated through natural (untrained) trial-to-trial variations in behavior. 3-D eye and head orientations were recorded and 2-D response field data were fitted against multiple models using a statistical method reported previously (Keith et al. J. 2009). Of 60 neurons, 17 showed a visual response, 12 showed a motor response and 31 showed both visual and motor responses. The combined visual response population (N=48) showed a significant preference for Te coding, which was also preferred in each visual sub-population. In contrast, the motor response population (N=43) showed a preference for final (relative to initial) gaze position models, and the Te model was statistically eliminated in the motor-only population. There was also a significant shift of coding from the visual to motor response, even within visuomotor neurons. These data confirm that the SC uses a gaze-centered frame, and show a target-to-gaze transformation between visual and motor responses. This shows that visuomotor transformations can occur between, and even within neurons within a single frame of reference and brain structure.

2.2 Introduction

The superior colliculus (SC) is involved in the transformation of visual signals into motor commands for gaze shifts (Wurtz and Albano 1980, Sparks and Hartwich-Young 1989, Sparks and Mays 1990, Everling, Dorris et al. 1999, Sparks 2002, Gandhi and Katnani 2011). Neurons in the superficial and intermediate layers respond to visual stimuli (visual neurons) whereas the intermediate and deep layers also (or only) show saccade-related activity (visuomotor, and motor neurons) (Wurtz and Goldberg 1971, Cynader and Berman 1972, Goldberg and Wurtz 1972, Wurtz and Goldberg 1972, Wurtz and Goldberg 1972, Sparks 1975, Sparks 1978, Munoz and Wurtz 1995). These layers form closely-aligned topographic visual and motor maps (Sparks 1986, Sparks 1988, Marino, Rodgers et al. 2008), and many individual cells show congruent visual and motor response fields (RF) (Sparks and Hartwich-Young 1989, Hartwich-Young, Nelson et al. 1990, Marino, Rodgers et al. 2008). However, none of these factors (i.e. temporal segregation of visual and motor responses, topography, or RF structure) directly show what spatial parameters (i.e., stimulus location, vs. gaze eye or head movement parameters, in various frames of reference) are coded within SC activity.

This is the question addressed in the current study, specifically: what spatial parameters are coded within SC visual and motor bursts during head-unrestrained gaze shifts to remembered visual stimuli, and how are these signals transformed through different identified cell types? Based on SC physiology and anatomy, one might expect visual responses (in visual and visuomotor cells) to encode the location of a target relative to the eye, like the retina (Cynader and Berman 1972, Marocco and Li, 1977, Berson 1988, Snyder 2000), but motor responses (in visuomotor and motor cells) might encode a variety of different spatial parameters. Motor

responses might still encode stimulus location (Sparks 1989, Frens and Van Opstal 1997, Edelman and Goldberg 2002, Quessy, Quinet et al. 2010), or they might code movement direction (Everling, Bell et al. 1999, Everling, Dorris et al. 1999). If movement direction, they might preferentially encode eye + head gaze displacement (Munoz, Pelisson et al. 1991, Freedman and Sparks 1997), or they might show separate eye vs. head signals (Cowie and Robinson 1994, Cowie, Smith et al. 1994, Walton, Bechara et al. 2007, Monteon, Avillac et al. 2012). Finally, gaze, eye, or head commands must be defined in some frame of reference (Crawford et al. 2011). Some early studies suggested that space-fixed goals are coded in the posterior SC (Guitton et al. 1980, Roucoux et al. 1980, McIlwain 1986), but most head-restrained (Cynader and Berman 1972, Sparks 1978, Sparks 1989) and head-unrestrained studies (Klier, Wang et al. 2001, DeSouza, Keith et al. 2011) have emphasized eye-centered codes.

To our knowledge, no previous study has established the difference in spatial coding between SC visual and motor responses in head-unrestrained conditions. This is particularly difficult to address because target, gaze, eye, and head motion tend to co-vary, and 3-D eye and head orientations are too variable (torsionally, vertically, and horizontally) for a conventional reference frame analysis. However, we recently developed a way to test between *all* of the possibilities listed in the preceding paragraph, simply by quantifying the goodness of fit between variations in neural responses and RF models derived from normally variable gaze parameters (Keith, DeSouza et al. 2009). We previously used this method to show that the SC population response preferentially encodes target location relative to initial eye orientation during gaze saccades made immediately to visual targets (DeSouza, Keith et al. 2011). Here, we probed SC physiology more deeply through the use of improved task parameters, additional models (for

gaze, vs. eye, vs. head motion), and most importantly, a memory-delay paradigm that allowed us to discriminate visual and motor responses, and trace their spatial codes through visual, visuomotor, and motor cells (Sajad et al. 2014).

2.3 Materials & Methods:

Surgical Procedures for Neurophysiological and Behavioral Recordings

The data were collected from two female *Macaca mulatta* monkeys (M1 and M2, Age: 10, Weights: 6.5 kg and 7 kg) using a protocol approved by the York University Animal Care Committee (ACC) in accordance with guidelines published by the Canadian Council for Animal Care (CCAC). Through surgical procedures described previously (Crawford, Ceylan et al. 1999, Klier, Wang et al. 2001, Klier, Martinez-Trujillo et al. 2003) the animals were prepared for long term electrophysiology and 3D gaze movement recordings. Each animal underwent general anesthesia with the aid of 1-2% isoflurane after intra muscular injection of ketamine hydrochloride (10mg/kg), atropine sulfate (0.05mg/kg) and acepromazine (0.5 mg/kg). During the surgery we implanted a vertically aligned unit recording chamber (i.e., with no tilt) placed at 5 mm anterior and 0 mm lateral in stereotaxic coordinates which allowed access to left and right SC. This chamber angle and position were chosen to minimize collisions between the electrode / microdrive and the experimental setup during head movements, and simplify the use of stereotaxic coordinates during recordings. The chamber was then surrounded by a dental acrylic cap which was anchored to the skull by 13 stainless steel cortex screws. Two scleral search coils (diameter 5mm) were implanted in one eye of the animals to record 3-D eye movements. Two orthogonal coils which were secured by a screw on a plastic base on the cap recorded the 3D

head movements during the experiments. 3D recordings and analysis were performed as described in our previous papers (Crawford et al. 1999; DeSouza et al. 2011).

Experimental Equipment

We used a Pentium IV PC and a custom designed software to present stimuli, control behavior paradigms, send digital codes to a Plexon data acquisition system, and deliver juice rewards to the monkeys. Stimuli were presented on a screen 60 cm in front of the animal, using a projector (WT600 DLP projector, NEC). Monkeys were seated on a custom-designed primate chair in order to have their heads move freely at the centre of a one meter cubic magnetic field generator (Crawford, Ceylan et al. 1999) and a juice spout (Crist Instruments) was placed on the skull cap for a computer-controlled delivery of the juice reward to the monkeys' mouth.

Behavioral paradigms:

In order to separate visual and motor responses, monkeys were trained to perform memory-guided gaze shifts. First, animals looked at a fixation point near the center of the screen which was a green circle with radius of 0.5 degrees (deg). The fixation light remained on for another 400-700 ms in order to introduce a variable memory delay and discourage anticipation of the go signal which was the disappearance of the initial fixation point. After 300 ms, a target stimulus appeared (red circle with size of 0.5 deg) in the periphery for 125 ms. When the go signal was presented the monkeys made a gaze shift toward the remembered location of target, and were required to maintain fixation for at least 200 ms at that final position to obtain the juice reward. The fixation light remained on for another 400-700 ms in order to introduce a variable memory delay and discourage anticipation of the go signal. The proper maintenance of initial fixation was

ensured by setting a tolerance window of 2-4 deg (radius) with respect to the fixation position. In order to spatially separate targets versus gaze coding, we allowed a tolerance window of 6-12 deg diameter for gaze errors around remembered location of the targets, and thus allowed monkeys to produce a natural (i.e. self-selected) distribution of gaze end points around the targets (Figure 2.1).

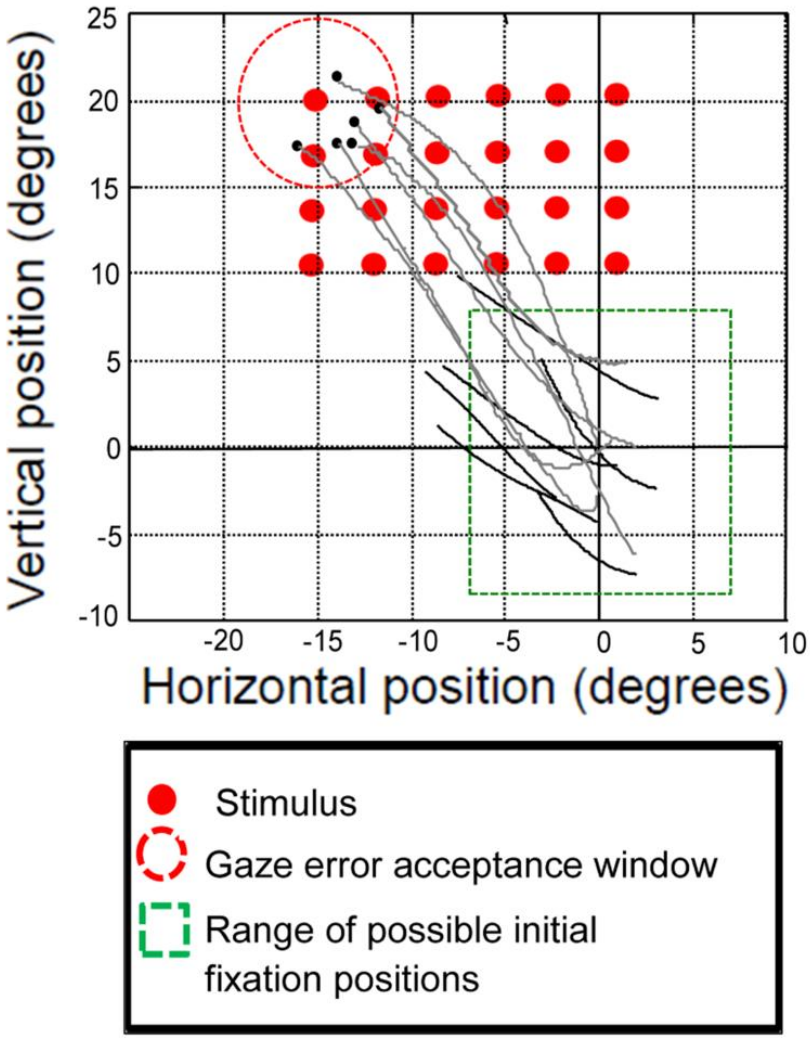

Figure 2.1- Example stimulus (red circles) locations and gaze/head trajectories. For this example, the red circle on top left corner was the target. Other possible targets for other trials are also shown but were not presented at the same time. The initial fixation position was randomly varied within a range approximately similar to RF of the isolated neurons (green square). Gaze errors were tolerated (i.e. rewarded) if gaze landed within a certain distance from the target (6-12 deg range for all experiments and 8 deg in this example). The head and gaze trajectories toward the example stimulus also are shown by black and grey lines respectively. The variation in initial position also led to various eye and head trajectory lengths and directions for a given target and helped dissociate eye, head and space coordinates (See Materials and Methods).

During experiments the target stimuli were presented in the visual field contra-lateral to hemi field of the recording site (see *neural recording*). Once a neuron was isolated, the RFs were estimated through initial mapping, which involved monkeys performing visually guided saccades to a wide range of stimuli presented on the screen while monitoring cell activity on-line. Test stimuli were then selected within a grid (12-32 targets depending on the RF size) that extended just beyond the cell's receptive field. During testing, stimuli were presented in a randomized order and each target was presented for least 7 successful gaze shifts. The initial fixating point was varied randomly from one trial to another within a square range approximately equal to the cell's RF size (Figure 2. 1). This variation led to a greater variation in initial 3-D gaze, head and eye positions, compared to DeSouza et al. (2011). Otherwise, animals were allowed to vary initial combinations of 3-D eye and head orientation (Figure2. 2 *left and center columns*) and the relative amount of eye and head contribution to the gaze shift (Figure 2, *right column*) as they wished. Note that in our animals the head contributes to nearly all size gaze shifts, perhaps because we did very little training with the head fixed. For example, in Figure 2H, one can see that the head moves for every size gaze shift (panel G), even when accompanied by very small eye movements (panel I). Figure 3A shows example data for the complete head movement

associated with the same gaze shifts (and return head movement), whereas Figure 3 B, C show the complete distributions of eye and head displacement (both contribution to gaze and full head movement) for our entire data set, with statistics in the Figure Legend. Note that our analysis method (described below) relies on the trial-to-trial variability of these parameters, not their amplitude. This is illustrated in figure 3 D by plotting the standard deviation of eye, head contribution to gaze and full extent of head movements as a function of stimuli locations on screen, the overall trend shows that the variability is maintained regardless of the location of stimulus and thus does not depend to amplitude of gaze shifts. The variability of head movements for given target locations are illustrated in figure 3E, which shows that for different stimulus location and head movements the trial-to-trial variations are present.

As a result of these simple manipulations and the naturally variable behavior produced by the monkeys, every neuron that we report below was tested with a variety of initial 3-D eye and head orientations, final target positions, final gaze positions, and different combinations of relative eye and head motion during the gaze shift. This provided the behavioral basis for the spatial separation between the models described below.

Trial definition and Inclusion Criteria:

The beginning of a trial was marked by the appearance of the initial fixation point. The beginning of the gaze saccade was defined as the instant that its velocity exceeded 50°/second (s) and its end when velocity decreased to 30 deg/S. The contribution of the head movement to gaze is defined here as the head movement from the start to the end of the gaze saccade. However, the head movement was often prolonged after the saccadic component of the gaze shift. Head

movements were marked from the start of gaze movement until the point at which head velocity decreased to below 15 °/s. For trials in which the head velocity never exceeded 15 °/sec the head position was sampled at the time of gaze onset and offset. The head movement marks were then visually inspected to ensure correct marks. For analysis, all trials were considered for analysis irrespective of whether or not the animal received reward after the trial. We excluded trials based on spatial and temporal criteria: First, trials in which the direction of the gaze shifts were completely unrelated to the direction of the target (i.e., say opposite direction) were removed. Then, we obtained the regression between errors in gaze vs. retinal error (note: retinal error is the retinal angle between the fovea and the target at the initial position before the gaze shift) and removed trials with gaze error 2 standard deviations greater than this regression line. Further, every trial was visually inspected, and any trial in which the gaze shift was anticipated (reaction time < 100ms after go-signal), consisted of multi-step saccades, or there was a saccade or head movement (> 5º) during the memory-interval, was excluded. The timing of the saccade was tightly linked to the time of the go signal, and was not influenced by the duration of the variable delay period: the correlation between the variable delay period and the reaction time of gaze shifts to the go signals was very low (0.11 for M1, p=0.62 and 0.012 for M2, p=0.24). Finally, for each neuron we required successful performance for at least 80% of total trials (mean+/- SEM trials= 162±28), and at least 7 successful gaze shifts toward each target location (with a possible maximum of 15, after excluding erroneous trials), and the neuron had to remain isolated throughout the recording session.

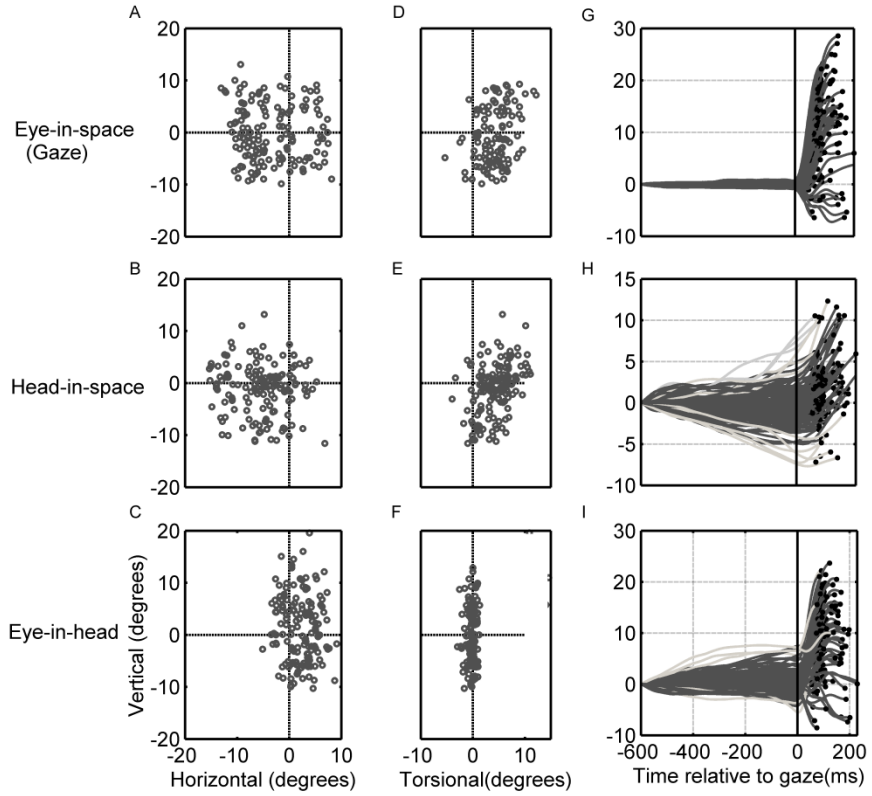

Figure 2.2- Behavioral parameters used in our analysis. Horizontal and vertical variations in initial fixation position (circles) of gaze (A), head (B) and eye (C) along with the torsional components (D-F) are illustrated for the same experimental session as Figure 1. In the right column the vertical component of gaze (G), head (H) and eye (I) movements are aligned with time relative to gaze onset, which shows variations in final vertical positions.

Neural recordings

We recorded extracellular activity from the left and right SC using tungsten microelectrodes (FHC). The electrode was inserted through a guide tube which was controlled by a hydraulic micro-drive (MO-90S, Narishige International USA). Isolated signals were amplified, filtered and stored for off-line sorting using Plexon MAP system. The SC was identified using criteria published previously (Klier, et al. 2001, DeSouza et al. 2011). This included the following steps: 1) Stereotaxic placement of the recording chamber, 2) on-line calibration of the stereotaxic coordinates through recordings of additional small midbrain structures with highly characteristic firing patterns and 3-D stimulation results, such as the interstitial nucleus of Cajal, 3)

advancement of electrodes in a search pattern based on the expected stereotaxic coordinates of the SC, 4) search for neural activity related to presence of visual stimulus and gaze onset, 5) preliminary on-line mapping of visual and motor response fields,(RF) and confirming that the observed RF, follow the SC map 6) low-threshold, head-fixed microstimulation of sites (at start and end of experiment) to confirm that saccades or stair-case saccades with zero torsion were elicited, 7) off-line analysis of results, and 8) confirmation across experiments of the orderly rostro-caudal and medio-lateral map of response fields and stimulation-evoked movements characteristic of the SC. In addition, recording sites have now been histologically confirmed in one animal. Cells that showed a clear response time-locked with the visual stimulus, saccade, or both, were recorded for off-line analysis.

Unit analysis and classification

After offline spike sorting, neural activity was aligned with experimental events in order to classify the type of activities and neurons (see Figure 4). Visual neurons (Figure 4 B) were defined as cells that showed a robust burst of activity (higher than 50 spikes/s above the baseline) 40-60 ms after the stimulus presentation that lasted for about 180 ms afterwards (Goldberg and Wurtz, 1972). Motor Neurons (Figure 4 E) were those with robust activity or a buildup of activity peaking at the time of gaze onset with activity starting prior to the gaze onset (100 to 40ms before saccade) and which continued to about 100 ms after gaze onset. Neurons that met both these criteria were classified as visuomotor (Figure 4 C/D). For visual neural activity a fixed temporal analysis of 60-160 ms (with respect to target presentation) was used (Figure 4 B/C), and for the motor neural activity a fixed temporal window of -50 to +50 ms (relative to gaze onset) was used (Figure 4 C/D).

For this analysis we only included head movement data up to the end of the gaze shift in our head-related model fits (see next section). We also analyzed motor activity in a variable window that included the entire duration of the movement-related burst of each neuron. For this analysis, we included the entire head movement in our model fits (see below). When we refer to 'number of spikes' below, this refers to number of action potentials in these defined temporal windows.

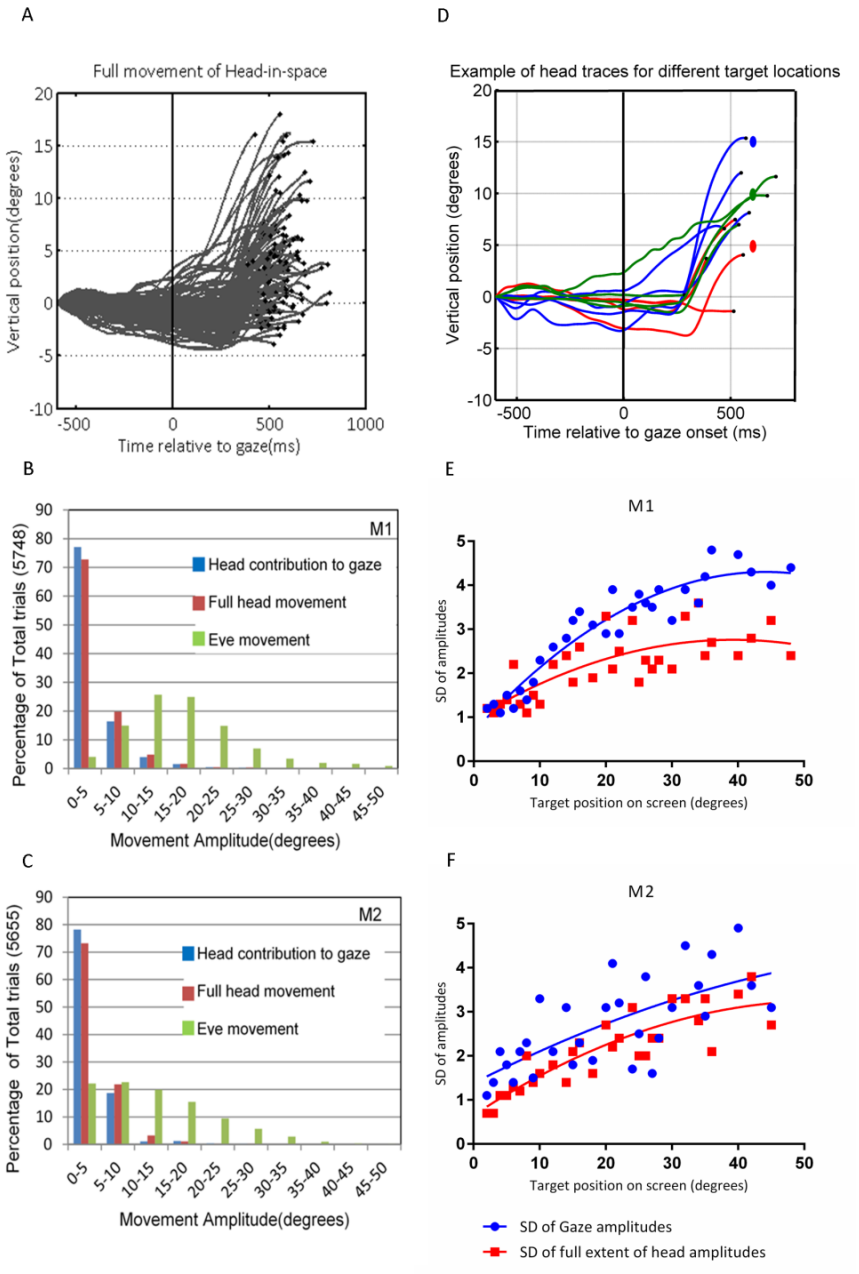

Figure 2.3- Details of eye and head amplitudes in our data set. A) The vertical component of head movement is plotted as function of time for the same trials as the one illustrated in figure 2H, but showing the head movement, with the greatest extent of the (full) head movements associated with the first gaze shift indicated by the dark dots. B) Frequency histogram of eye (green), head contribution to gaze (blue) and full head movement (red) amplitudes for subject M1. For this animal the statistics for eye, head contribution to gaze and full head movement (respectively) in degrees were: mean amplitude (17.36, 1.86, 2.44), median amplitude (16.00, 0.90, 1.30), minimum (1.90, 0.00, 0.00), maximum (50.30, 43.30, 45.19), lower quartiles (11.20, 0.40, 0.52), upper quartiles (21.40, 2.20, 2.86). C). Frequency histogram of eye (green), head contribution to gaze (blue) and full head movement (red) amplitudes for subject M2. For this animal the statistics for eye, head contribution to gaze and full head movement (respectively) in degrees were: mean amplitude (12.85, 3.10, 4.37), median (11.10, 1.70, 2.64), minimum (1.70, 0.00, 0.00), maximum (49.50, 37.90, 45.48), lower quartile (5.50, 0.60, 1.32) upper quartile (18.20, 4.10, 6.13). D) Example of trajectories for head movements toward different vertical target locations: 5º (red), 10º (green) and 15º (blue), note the variations in amplitude of head movement for a given target location. E) Standard deviation of eye (95% confidence interval: 1.65) and full extent of head movement (95% confidence interval: 0.82) amplitudes are plotted as a function of target distances from centre for subject M1 F) Standard deviation of eye (95% confidence interval: 1.70), and full extent of head movements (95% confidence interval: 0.73) are plotted as a function of target distances from centre for subject M2

We used a method previously reported by Keith et al (Keith, DeSouza et al. 2009) and DeSouza et al. (DeSouza, Keith et al. 2011), with further optimization of the behavioral method for the analysis (Fig.1) and the addition of effector-specific models, i.e., eye movement relative to the head and head movement relative to space (Fig. 5). This approach allowed us to simultaneously test between different models without any special training (other than the delay fixation training), relying instead on the animals' natural variability in behavior (Figs. 1 and 2). In short, we plotted the RFs of neurons' visual and motor activity in various representations to identify the model which gave the most coherent fit, i.e., the least variability in number of spikes for a given spatial location, as illustrated schematically in Figure 5B.

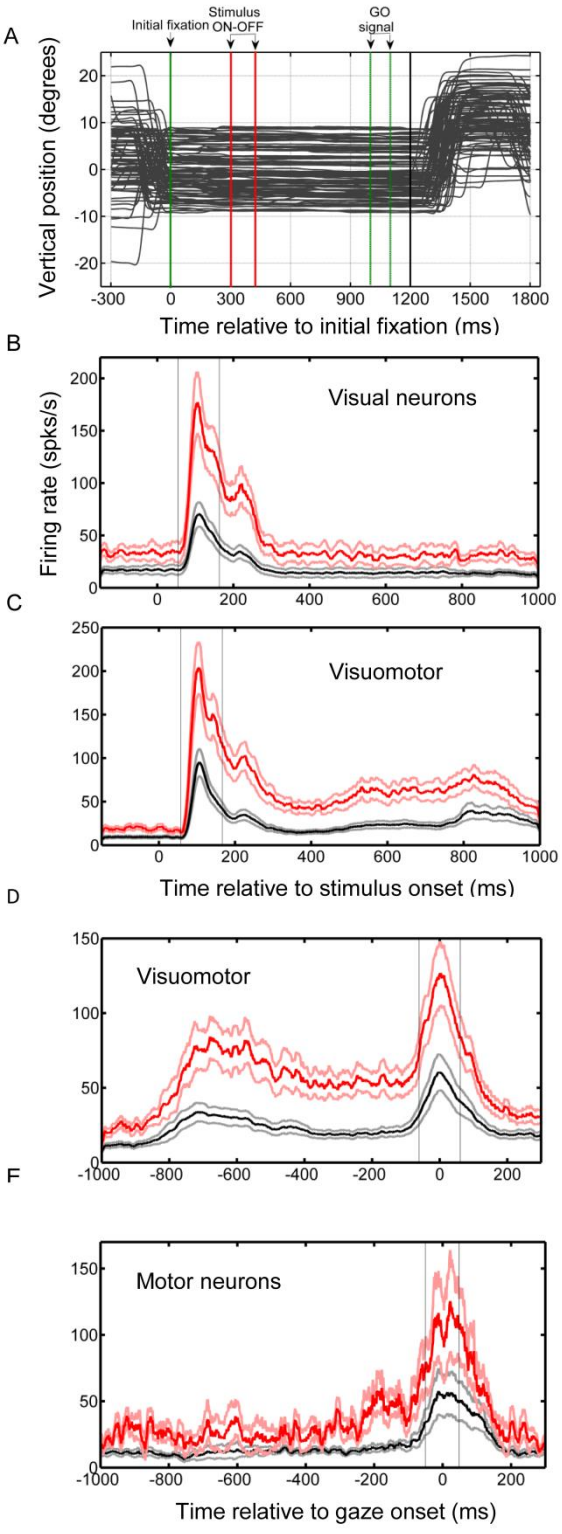

Figure 2.4- memory guided saccade paradigm and population responses of visual, visuomotor, and motor cells. A) Vertical eye positions aligned with experiment events. The black vertical line after the gaze onset represents the reaction time gaze inclusion criteria (RT>100ms). B) Spike density plot for visual neurons aligned with stimulus presentation, C) visual activity of visuomotor neurons aligned with stimulus presentation, D) Motor activity of visuomotor neurons aligned with gaze onset and E) Motor activity of Motor neurons aligned with gaze onset (E). The average number of spikes (black) across all recorded neurons of the type, with confidence intervals (light grey) and the top 10% number of spikes (red) with confidence intervals (light red) are shown here. The sampling windows for visual (60-160 ms after stimulus onset) and motor (±50 ms relative to gaze onset) are represented by vertical light grey lines.

Experimentally, this was quantified by the mean predictive sum of squares (PRESS) statistics. PRESS residuals were obtained by computing the residual for each trial relative to fits obtained from all of the other trials. The "best fit" for the activity of a given neuron was defined as the smallest overall mean residual of the PRESS obtained from fits between number of spikes obtained from all trials, compared across all models, and across all bandwidths (the width of the convolution kernel used in fitting the data to each model). This method –compared to traditional regression techniques- has the advantages that it makes no assumptions about shape of the RF or linearity, and utilizes the full 2D range of the neural RF and 3D range of eye and head kinematics (Keith, DeSouza et al. 2009, DeSouza, Keith et al. 2011). These factors are all important in this study, because RFs in the SC are neither simple nor linear (e.g., Figures 7, 9, 10, 11), and most of the models described below are inherently non-linear and/or depend on 3-D eye or head orientation (Martinez Trujillo et al. 2004).

Here we summarize all the models which are included in our analysis (Figure 5 A):

Target Models: In these models we were testing if neural activity encoded target location relative to initial 3D eye orientation (Te), head orientation (Th), or in the space-fixed (or body fixed) coordinates (Ts).

Gaze Models: Here we tested if neural activity encoded the final gaze position relative to initial eye orientation (Ge), to head orientation (Gh) or relative to space coordinates (Gs).

Displacement models: These models consider the possibility of neurons encoding the vector displacement (i.e. final position minus initial position) of the eye during gaze shifts (i.e. the

saccade) (dE), Gaze in space (i.e. gaze displacement vector as projected onto a 2D screen) (dG) or the head in space (dH).

Final eye and head position models: We tested models corresponding to the head's final position in space (Hs) or that of eye position in orbit (Eh) (note that some of these models may be quite similar spatially). For example, Ge and dG are both 'gaze-centered' in the sense that the zero reference position is initial gaze direction, but the coordinates of Ge are fixed in the eye whereas the coordinates of dG are fixed in space (Crawford and Guitton 1997). The difference between them only becomes evident for large deviations in eye orientation (torsion, vertical, or horizontal) combined with large gaze shift components in an orthogonal dimension (Klier, Wang et al. 2001). Further, both resemble dE when eye displacement dominates the gaze shift (Freedman and Sparks, 1997). We derived visual and/or motor RFs for each of our neurons for all of these models, by plotting the number of action potentials in our sampling windows (Figure 4) for each trial as a function of the horizontal and vertical coordinates dictated by each of the above models as derived from our behavioral data for that trial. Contour fits were made to neural activity plotted as a function of the vertical and horizontal axes defined by each of these models, using a non-parametric method based on a series of Gaussian kernels ranging between 2-15 deg in steps of one (Keith et al. 2009). This method is robust for fitting various oddly shaped or discontinuous RFs, and thus avoids the problems inherent in fitting a simple Guassian shape to RF that do not have a Gaussian shape (Platt and Glimcher 1998). The model (and bandwidth) that yielded the minimum mean PRESS residuals was identified as the "best fit" model, and was statistically compared to all other models at the same bandwidth.

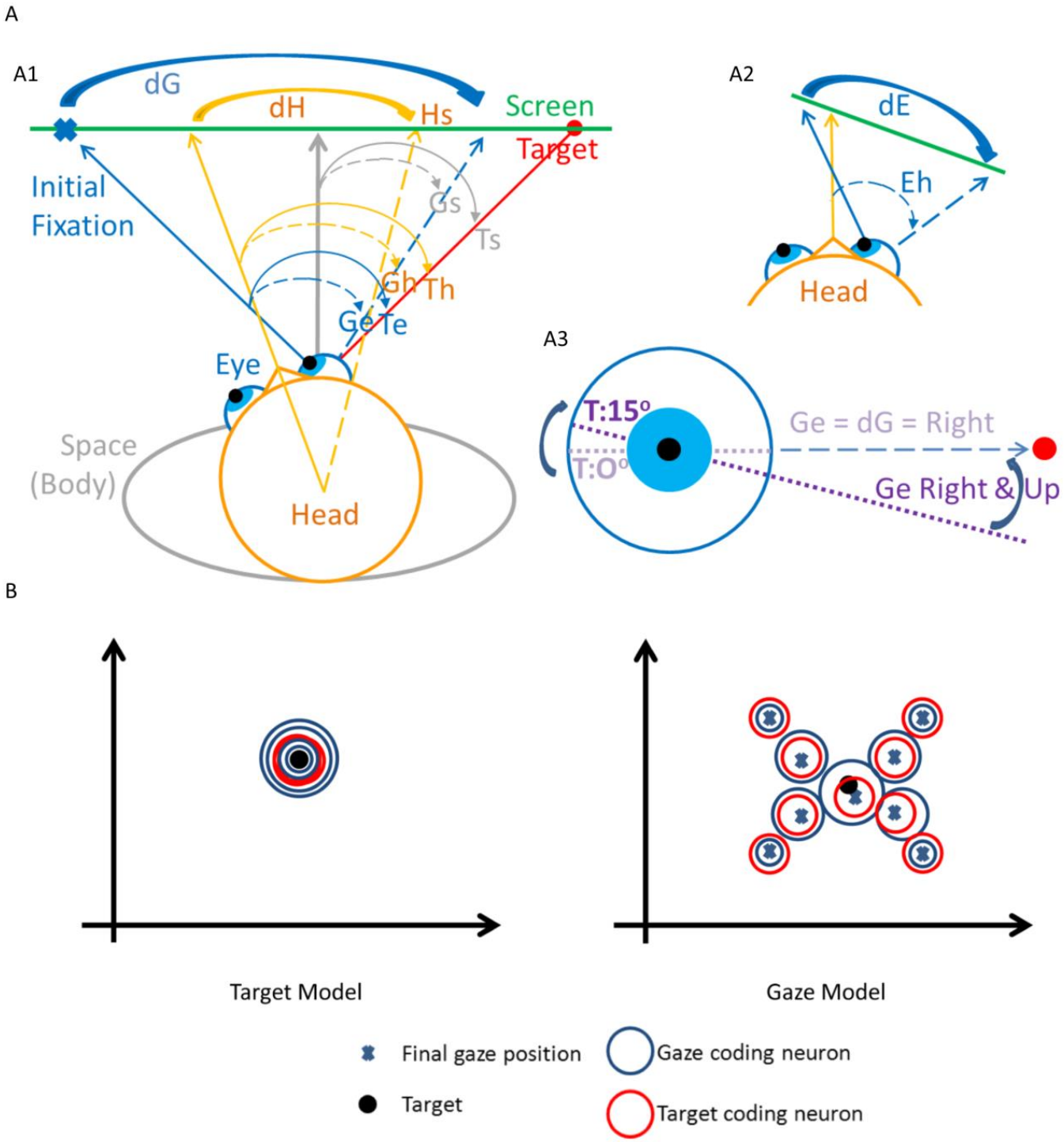
A
A1
dG
dH
Hs
Screen
Target
Initial
Fixation
Gs
Ts
Gh
Th
Ge
Te
Eye
Space
(Body)
Head
A2
dE
Eh
Head
A3
T:15°
T:0°
Ge = dG = Right
Ge Right & Up
B
Target Model
Gaze Model
Final gaze position
Target
Gaze coding neuron
Target coding neuron

Figure 2.5. A) Geometric Interpretation of models being tested. This hypothetical example shows the space-fixed body (*gray ellipse*), with the head (*orange ellipse*) and eyes (*blue circles*) turned to the left towards an initial fixation point (*blue cross*) on the screen (*green line*). The *solid red line and circle* indicate the direction of the target on the right side of the screen. Solid *blue*, *orange*, and *gray arrows* pointing toward the screen show initial pointing directions of gaze from the recorded eye, head, and body (fixed at midline) respectively. *Dashed orange and blue lines* pointing toward the screen show the final pointing direction of the head and gaze, respectively, after a future gaze shift. The heavy arrows show displacement of gaze (dG) and head (dH) pointing direction on the screen. A2) the conceptually similar displacement of eye-in-head (dE) is shown in head-centered inset (*right panel*). The *solid gray, orange, and blue arrows* cueing to the right show the angular position of the target relative to space (Ts), initial head orientation (Th), and initial eye orientation (Te), respectively. The *dashed gray, orange, and blue arrows* curving to the right show the angular position of final gaze relative to space (Gs), initial head orientation (Gh), and initial eye orientation (Ge), respectively. Again, final head relative to space (Hs) is shown by the *straight dashed orange arrow*, and final eye position relative to the head (Eh) is shown in the *right panel*. All of these parameters were allowed to vary freely in our experiment, except that initial gaze and head orientations were kept in a more central zone (see Figure 2.2). Actual distances of the eyes from the screen are further than depicted here, so translational motion of the eyes is negligible and does not affect our analysis, which was based on trial-trial variability of angular body positions. A3) the bottom right panel illustrates the dissociation of some of the models which can occur in very large gaze shifts. For example, in very large gaze shifts there's significant torsional movement of the eye which dissociates the two dimensional vector of gaze displacement (dG) from the displacement of the gaze in retinal coordinates (Ge) which depends on the position of the target on the retina and thus as the eye rotates the Ge vector changes whereas the dG vector remains the same. B) Schematic diagram of tuning of two different neurons for two different spatial locations gaze end points vs. target location. The number of spikes is proportional to diameter of circles for both target coding neuron (⭕) and the gaze coding neuron (⭕). The figure on the left shows the number of spikes of these two neurons for a given target location(●), the target coding neuron fires consistently at a high rate, however the gaze coding neuron fires at different rates for each trial. Thus the number of spikes of target coding neuron is more "coherent" in this example. The figure on the right shows that the number of spikes for the gaze coding neuron increases systematically for the preferred gaze end point location (X at the center), whereas the number of spikes of the target coding neuron does not change with different gaze locations.

Specifically, a two-tailed Brown-Forsythe test was used to compare the PRESS residuals of the "best fit" model with each of other models. The model that resulted in significantly greater PRESS residuals was excluded. The analysis also accounted for the presence of any "gain fields" (i.e. gaze position-dependent modulations) effects but we found no significant gain field effects

here, perhaps due to limitations in the range of initial gaze position. Note that the mean PRESS residuals were never reduced to zero for any model, likely because of non-spatial factors that were not accounted for in our models such as attention, motivation and/or random biological noise. The last step in our analysis involved combining the results of individual neurons in order to provide an overall measure of the best model fit for population of visual and motor activities See (Keith, DeSouza et al. 2009).

Because of the predominance of Te and eye-centered gaze codes (i.e., dG and Ge) in our results (Figs 6 and 8.), we constructed a continuum between Ge and Te models to test "intermediate" Te-Ge models. This involved the calculation of PRESS residuals for models along 10 steps between and 10 steps beyond each side of these two models and identification of the overall best fit (Sajad, Sadeh et al. 2015). We selected Ge over dG because it is in the same reference frame as Te, and as a result, the constructed continuum would provide physical locations between target and gaze positions relative to the same reference frame (fixed on the eye). Te and Ge models were positioned at -5 and 5 on the continuum in each trial. The spatial models beyond Te and Ge (from -5 to -15, and from +5 to +15) were constructed to prevent false clustering at the two canonical representations. Theoretical and experimental studies have shown that individual neurons can show fits that go beyond the intermediate range between two models, i.e. further away from Ge than Te, or further away from Te than Ge (Patel, Kaplan et al. 2014).

Finally, note that our analysis does not account for other factors that might modulate SC activity, such as eye velocity (Munoz et al. 1991, Goossens and van Opstal 2012), motivation levels (Isoda and Hikosaka 2008), attention levels (Goldberg and Wurtz 1972, Shen et al. 2011), plans for future

gaze shifts or head movements (Monteon et al. 2012), or influences of eye position that do not reach statistical significance in our program (Van Opstal et al. 1995,DeSouza et al. 2011), or completely random biological noise. For this reason, none of our spatial models can be expected to reduce the residuals of fit to zero for any neuron; we can only determine the best spatial fit.

2.4 Results

Neuron population

We recorded from 78 neurons from left and right superior colliculus of two monkeys, and 60 of these neurons met our inclusion criteria (see Materials and Methods). These neurons showed both 'closed' RFs (with boundaries defined within the range that we tested) and 'open' RFs (with boundaries that extended beyond the range where stimuli could be presented) with peaks varying from 4-30º from the fovea (see Figures 7, 9, 10, and 11 for examples). Based on the criteria described above, 17 of these neurons were classified as visual, 12 were classified as motor neurons, and 31 were categorized as visuomotor neurons.

Figure 4 summarizes the average (+/- SEM) spike density profile for all neurons, either derived from all trials (black / gray lines) or from the neural response for trials with top 10% number of spikes (measured in the specific time epoch explained above) (red / pink lines). The latter corresponds to trials toward the RF "hot spot" in the preferred representation of the RF. These spike density profiles are aligned either with stimulus (B and C) or movement onset, (D and E). The plots show the mean and variability of both the amplitudes and durations of our visual and motor responses (see Methods). They also show the fixed temporal windows used to analyze the visual and motor responses. As noted in the Methods, we also used a variable motor window to

the motor burst duration of each individual neuron, which varied across neurons from -100 to +160 ms with respect to gaze onset. Both methods produced very similar results for individual neurons and at the population level (shown in Figure 8), so unless stated otherwise, the fixed window analysis was used to generate figures.

Note that our population motor response (and some of the individual neuron motor responses shown below) was lower than one might expect. This is likely because: 1) we show the number of spikes of motor neurons using the top 10% activity surrounding the peak RF response, rather than repeating saccades to the absolute peak, 2) because head unrestrained gaze shifts are often accompanied by longer, less intense motor bursts than head restrained saccades (Freedman and Sparks 1997 a and 1997b; Choi and Guitton 2006; Choi and Guitton 2009; DeSouza et al. 2011; Monteon et al. 2012), and 3), memory-guided saccades are associated with less intense motor activity compared to saccades made directly to a visual transient (Stanford and Sparks, 1993; DeSouza et al. 2011).

The following sections examine each of these sub-populations (separately considering their visual and motor responses as appropriate), in order to establish which candidate models of their spatial coding scheme were preferred and which could be statistically eliminated. For reference, Figure 6 summarizes the % neurons that gave a best fit (red), the % neurons for which that particular model remained a possible fit (green; i.e., not statistically eliminated), and the % neurons that were statistically eliminated (blue), for each of the models tested, in each frame of reference.

Visual activity

Figure 7 shows the main results of our analysis of a representative visual neuron; this includes the spike density and raster plot for the trials which have the top 10% number of spikes (D), RF plots for three example models (A-C), PRESS residuals for all models fitted with kernels of different bandwidths (E) and the statistical comparison between models (F). In the RF plots, neural activity for each trial (represented by circle size, see Figure 5) are plotted over non-parametric model fits to these same data, indicated by the color-coded contours. The best fit corresponds to the model and bandwidth (in this example 2º) that gave the overall lowest residuals in Figure 7E, and the same bandwidth was used for the other RF plots. The residuals between the data (circles) and the color-coded fits are plotted at the bottom of each panel A-C (these residuals are equivalent to the vertical difference between individual data points and a linear fit in a standard 2-D regression analysis).

In order to visually illustrate the method and results for this neuron, we plotted the example neural data and their color-coded fits relative to A: target direction in space (Ts), which is roughly equivalent to target position on the screen, B: the model coordinates that yielded a significantly worse fit (Ge), and C: the model coordinates that yielded the best fit for this neuron (Te). This goodness of fit is explicitly indicated by the relatively small (positive or negative) residuals at the bottom of panel C compared to A and B. The poor fit for Ts and Ge models can also be visualized intuitively as overlap of both small and large circles (visual bursts) at the same spatial locations in A and B, whereas similar sized circles cluster together in the Te model (C), producing a more *coherent* plot with larger circles in the centre and smaller circles in the periphery (as explained in

Figure 5B). This is reflected as a central hot-spot in the color-coded non parametric fit for Te (C), whereas the fits appear 'washed out' in panels A and B.

The statistical analysis for this neuron is shown in Figure 7F, which provides P values comparing the residuals for the overall best model (Te fitted using 2º-bandwidth kernel), to those of every other model at that bandwidth. For this neuron, every other candidate model was statistically eliminated ($P < 0.05$). These observations held for most of our visual neurons (Figure 6 A). In 70% of these neurons there was a significant preference for Te, with most of the remaining neurons showing a non-significant preference for Te.

It is also important to determine what information is being encoded at the population level; therefore, we combined the results of single neuron analysis for the different populations in the study (see methods). The population analysis of visual neurons showed that the target relative to eye model (Te) is significantly better than of all the other models that we considered (Figure 8A), except the Ge and dG models, which were close to being statistically eliminated. These data indicate a clear preference for Te in visual neurons.

Visuomotor Neurons: Visual activity

Figure 9 shows an example analysis of visual activity of a representative visuomotor neuron, following similar conventions as Figure 6, but this time only showing A: the data points and color-coded RF fit for the Ts model as a control reference; the data points and color fit for the best RF model: the spike density and raster plot for the neuron's top 10% 'hot spot', and D: statistical comparisons to the best model. In this neuron Te still gave the best fit but now the Ge and dE models were not significantly excluded (Figure 9 D). Across all visuomotor neurons (Figure 6 B)

the visual response showed a preference for Te in most cases, and in 53% this preference was significant. At the visuomotor population level (Figure 8C) the visual response still preferred Te, but the statistical separation between Te, Ge and dG models showed less clear preference for the Te model than the visual response of purely visual neurons.

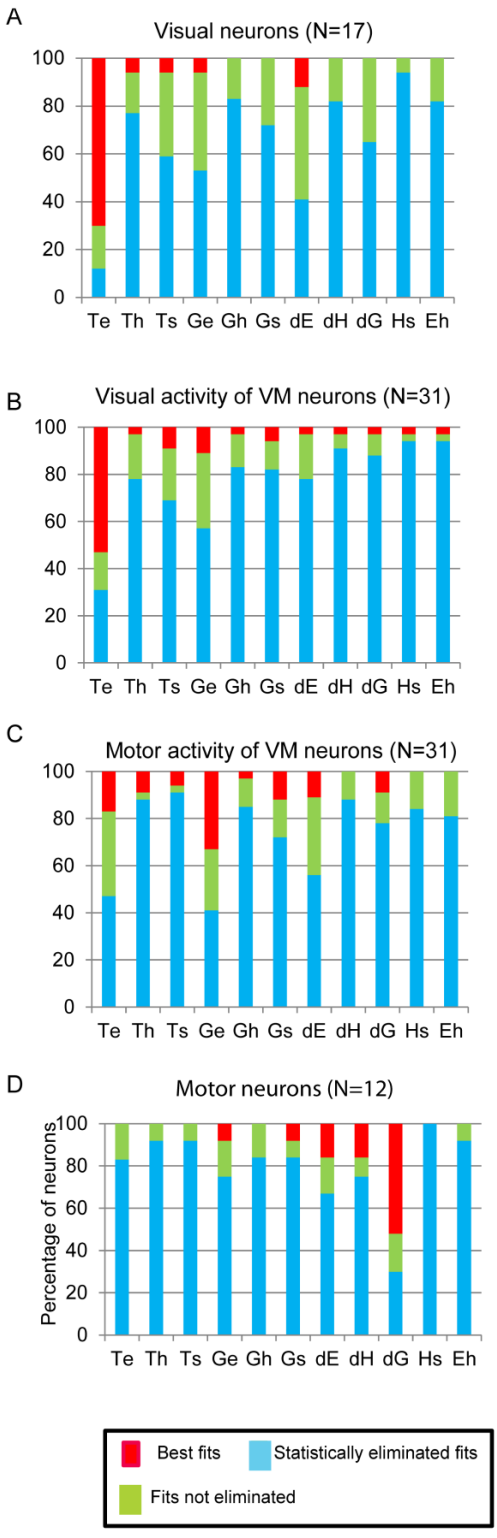

Figure2- 6- Frequency histograms of goodness of fit for each model across neurons in each cell type. Best models (red) are defined the models with the lowest residual compare to others. Possible models (green) do not possess the lowest residual but the residual of their fit is not significantly larger than the best fit and thus cannot be eliminated. Worst models (blue) are the models with residuals significantly larger than the best model and are thus significantly eliminated as a spatial coding possibility A) Distribution of results for visual neuron population, more than 60%of neurons have the Te model as their preferred spatial code. B) Distribution for visual activity of visuomotor neurons, which shows that the majority of neurons still prefer the Te model, however the percentage is now 36%. C) The motor activity of visuomotor neurons the percentage for best and possible fits at Te is decreased and the Ge has the highest percentage. D) In motor neurons the dG is the dominating model along with dE and Ge, with no neuron having its best model at Te.

Visuomotor Neurons: Motor activity

Figure 10 shows the main results of analysis of the motor activity of the same visuomotor neuron shown in figure 9. Once again, we have illustrated the fit for the Ts model for reference (A), for the best fit model (B), the spike raster and density plot for the neuron (C), and the key statistics in Figure 9 D. In contrast to the visual activity described above, where Te was clearly preferred, the motor burst showed a general preference for (but did not clearly discriminate between) several eye and gaze models (dE, dG, Eh, Gh, Ge), over Te, although the latter was not statistically eliminated. In other words, errors in final gaze position were reflected in variations in motor related number of spikes in these neurons, yielding a better overall fit than target position alone. Across all individual visuomotor neurons (Figure 6C), Ge was statistically preferred in the most (58%), but overall the preference for motor burst was more distributed amongst models compared to the visual burst analysis described above, with no clear statistically significant 'winner'.

For the population of motor activity in visuomotor neurons (Fig. 8 B), Ge produced the lowest residuals, but Te, dE and dG were very similar and were not significantly eliminated. This held for the fixed-window / head-contribution-to-gaze analysis (○) and the full-burst / full-head-movement analysis (●). This suggests a shift in coding tendencies between the visual to motor component of visuomotor neuron activity (Figure 8B/C), which we will quantify more directly in a subsequent section.

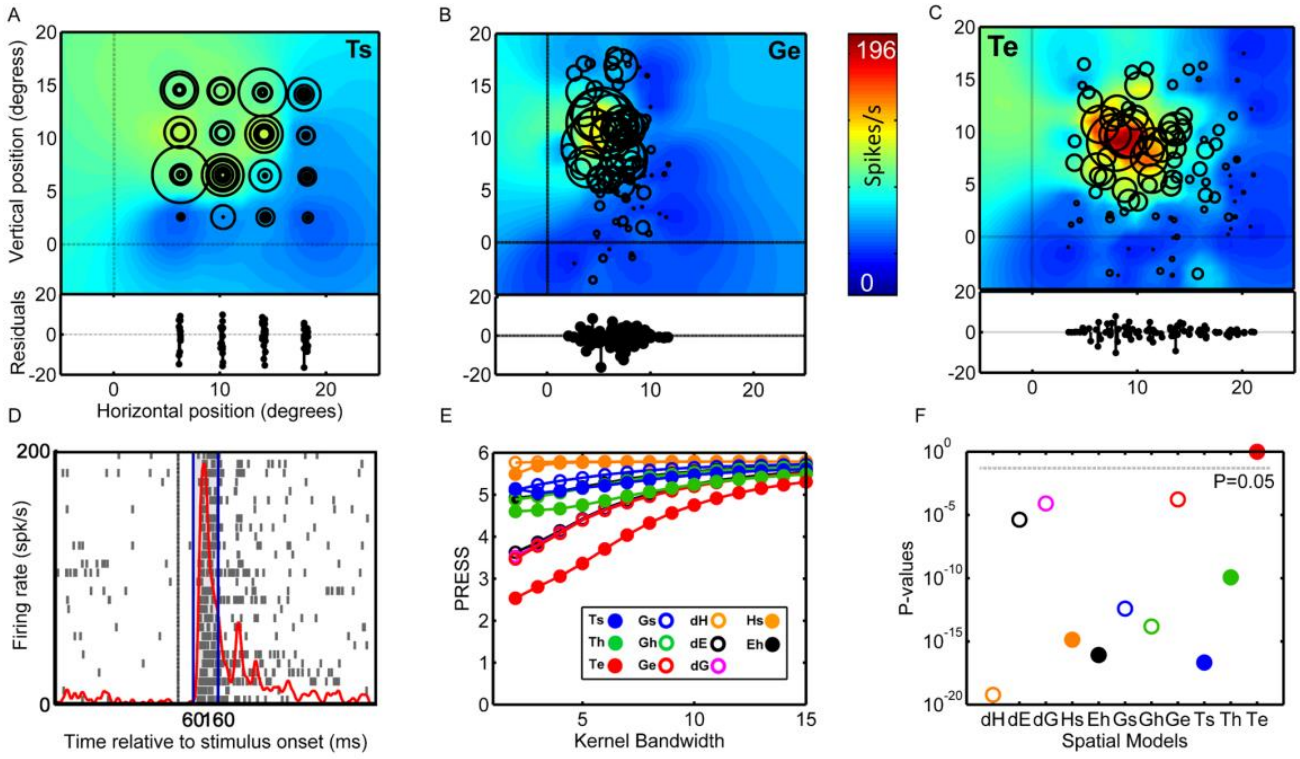

Figure 2.7– Example of the analysis for a representative visual neuron A) Response field (RF) plotted in target in space model (Ts) coordinates, the color code represents the non-parametric fit to the model. The center of circles represents the location of the targets in the Ts (i.e. the location of targets on the screen), and the diameter of the circles is proportional to number of spikes for that given trial. The bottom panels show the residuals from fit. B) Example of a RF plotted in final gaze relative to initial eye position models (Ge), which results in a poor quality fit (compare the size of residuals and circle size similarities) C) RF plotted in Target in eye model (Te), which results in a fit which has significantly smaller residuals. D) Spike density and raster plot for the top 10% number of spikes of this visual neuron. The sampling window is represented by vertical blue lines; alignment is represented by vertical black line. E) Comparison between

different models' PRESS values at the specified kernel bandwidths. F) Statistical comparison between the best fit and other models, dashed line represent the significant difference line, models represented below the p=0.05 have significantly larger residuals and are thus eliminated as a possible spatial code

Motor Neurons

Figure 11 summarizes the results of our analysis of a representative motor neuron using the same conventions as Figures 9 and 10. In some respects this neuron showed similar results to the visuomotor example shown above: the eye displacement model (dE) and several eye and gaze-related models (dG, Ge, and Gs) were preferred, without a clear distinction between them. But this time, unlike any neuron we have shown so far, the Te model was statistically eliminated compared to the gaze-related models. In other words, in motor neurons, fits that accounted for errors in final gaze position produced significantly lower residuals than fits that only accounted for the target location. This was the case in about 80% of the motor neurons tested (Figure 6 D). Across all neurons, dG showed the best fit in most cases, and in some cases this was statistically significant (Figure 6D). However, in the population analysis (Figure 8D) Ge and dG (which are geometrically very similar models) were nearly indistinguishable, as well as several other eye and gaze models. But importantly, Te was now significantly eliminated, for the first time, at the population level. This trend did not change when considering full burst and duration of head movement (●) compared to fixed window analysis (○). In addition, we have repeated the analysis for the motor activities with only including the trials that have head amplitudes of 5 degrees or greater; although this resulted in omission of more than 75% of our total number of trails and thus reducing the statistical power in our comparisons but we observed a similar trend of results with dG and Ge as the preferred models.

When the motor activity was combined into one population (Figure 8F), the dG and Ge models gave the best fits (and were nearly identical) along with dE and Te as candidate models. Again considering the full burst response (●) and head movement did not change in either trend or significant separation in the population (Figure 8F).

Summary and Combined Populations Analysis

To summarize the main results so far, the preferred models for all populations were gaze centered models, but we have seen a clear transition from Te being preferred in the visual burst (Figure 8 A, C) to gaze models being slightly preferred in the motor burst of visuomotor neurons (Figure 8 B) to Te being entirely eliminated in the motor-only population (Figure 8 D). To highlight the main visual-motor trends, we also did analysis of the combined visual populations and combined motor populations (Figure 8E and F). When the visual responses from both the visual population and the visuomotor population were combined (Figure 8E), the resulting population (N = 48) showed a statistical preference for the Te model over *all* of the other models that were considered. In the combined motor population (N = 43; Figure 8 F) the similar dG and Ge models were front runners (see Discussion), with the also similar dE model lagging not far behind, followed by the Te model, and all other models were statistically eliminated. We re-tested the full dataset after removing trials in which the head contribution to gaze was less than 2 deg. This analysis (not shown in the figures) produced nearly identical results.

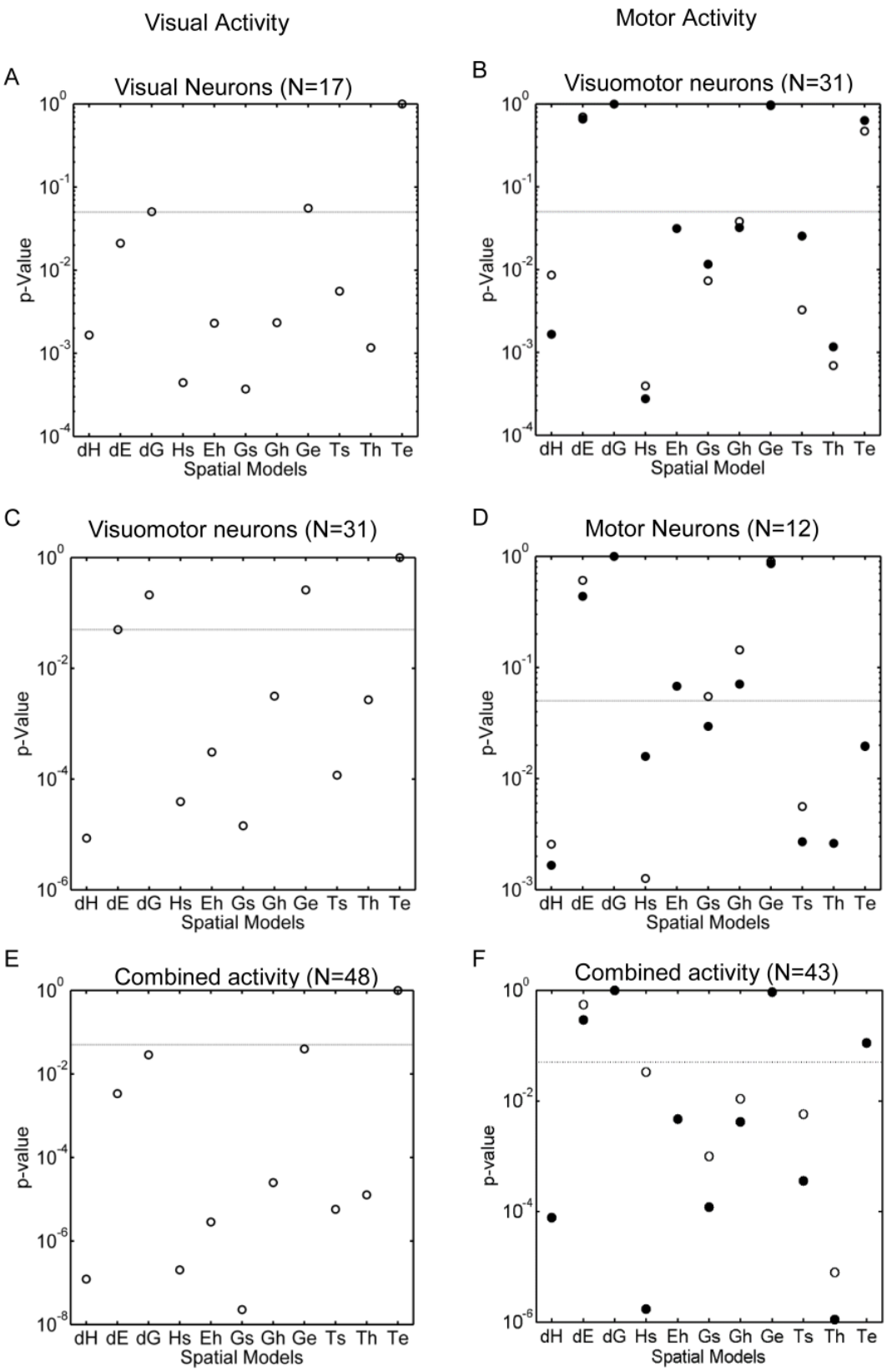
Visual Activity
Motor Activity
A
Visual Neurons (N=17)
B
Visuomotor neurons (N=31)
C
Visuomotor neurons (N=31)
D
Motor Neurons (N=12)
E
Combined activity (N=48)
F
Combined activity (N=43)
p-Value
p-value
dH dE dG Hs Eh Gs Gh Ge Ts Th Te
Spatial Models
Spatial Model

Figure 2-8- Results of population analysis for A) Visual neurons population which shows a clear separation between the Te model with other models, which is represented by the horizontal line at p=0.05, thus anything below this line has a significantly larger residual and is eliminated as a possibility, and anything above this line which is not the fit with smallest residual (i.e. the best fit), is still considered a possible spatial parameter which the activity is coding for. Results of visual neuron population suggest that this neuron population is encoding for location of the target in eye centered coordinates. B) Motor activity of visuomotor neurons, gaze related models are better than Te model which suggest a change in coding within individual visuomotor neurons C) Visual activity of visuomotor neurons, the best fit is still Te model but the separation with gaze related models is less so compare to visual neurons. D) Motor neurons, dG as best fit along with some other gaze related models are amongst possible coding schemes which is interestingly better than Te model which may be due to another level of visual to motor transformation from visuomotor to motor neurons. For C and D, analysis was also done with consideration of full motor burst and full duration of head movement; the results are represented by solid circles and in cases of similar results only solid circles are visible. E) Population analysis for combined activity of visual and visual compartment of visuomotor neurons, this indicates that coding for Te model is significantly preferred over all other models by the visual activity in SC. F) Population analysis for combined activity of motor activity of visuomotor neuron and activity of pure motor neurons, there is a trend toward coding for motor related models and the Te model is no longer the best fit.

Target-Gaze Continuum Analysis

To focus on the changes in spatial coding between our visual and motor responses, we developed a new continuum analysis between Te and Ge models. We used Ge here to represent the motor code because it uses the same mathematical frame as Te (but note again that Ge gives nearly identical results to the geometrically similar dG).

First, we considered how the placement of a neuron along this continuum related to the relative vigor of visual vs. motor bursts, by calculating a visuomotor index (VMI = (Motor spike count - Visual spike count / (motor spike count + visual spike count)). The visual and motor burst spike counts were first subtracted from the baseline activity (100ms pre-target period). This gave a score where -1 is a purely visual neuron and +1 a purely motor neuron). Neurons classified as

visual had VMI values ranging from -0.83 to -0.15, visuomotor neurons ranged from -0.74 to 0.44 and the pure motor neurons had VMI values from 0.2 to 0.94. Figure 12A shows the VMI plotted as a function of the Te-Ge spatial coding continuum for all neurons, and each sub population is color coded (Red: visual neurons, light red: visual activity of Visuomotor neurons, grey: motor activity of visuomotor neurons and black: pure motor neurons). This leads to a very weak positive correlation (R^2=0.1 for motor response and 0.01 for visual response) distributed, but one can see a general tendency for the visual responses to cluster in the lower-left, and motor neurons (especially in pure motor neurons) to cluster in the upper-right.

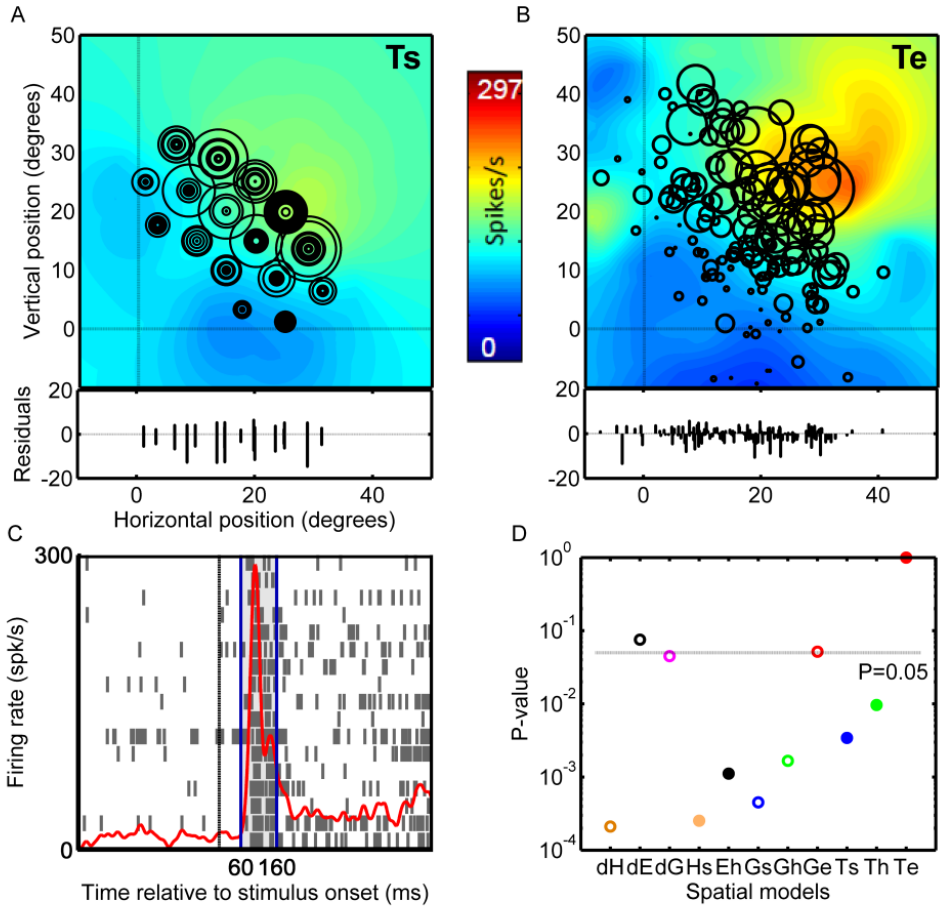

Figure 2-9– An example of visual activity analysis of a representative visuomotor neuron. A) RF plotted in Ts model coordinates B) RF plotted in the Te (Best fit). C) Spike density and raster plot for the visual activity of this visuomotor neuron D) Statistical results for model comparisons.

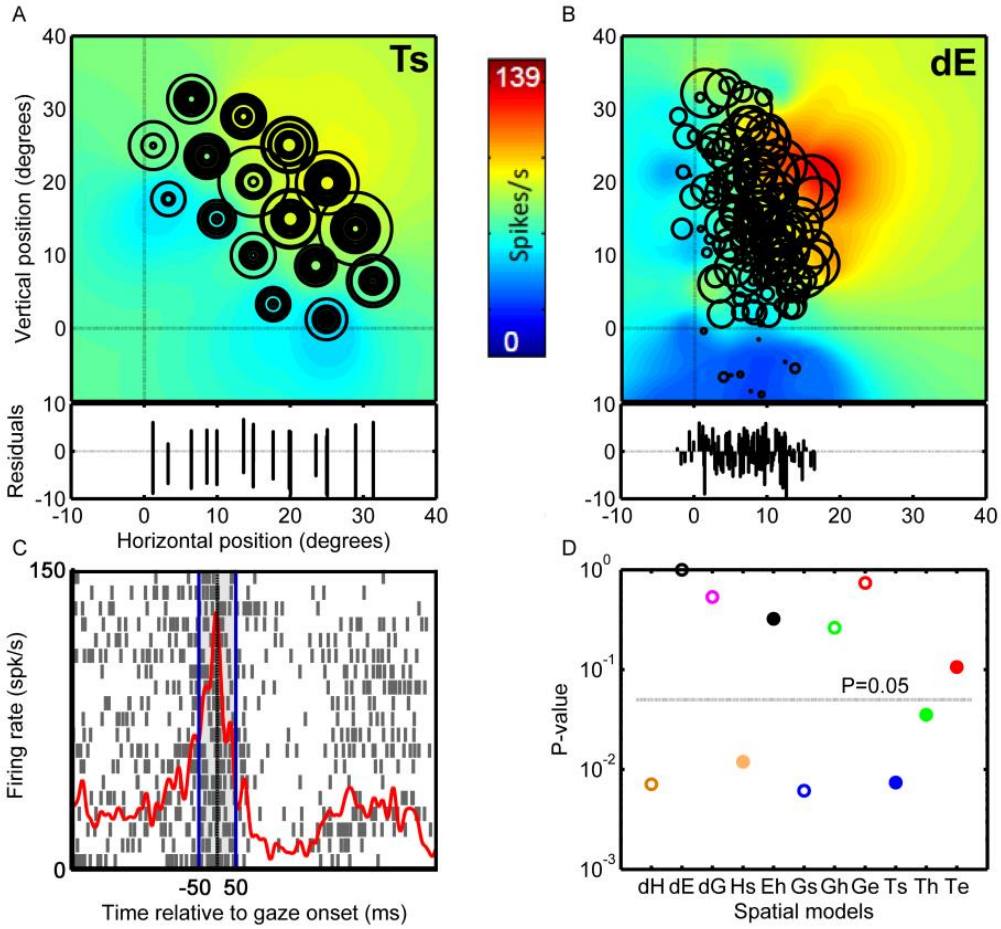

Figure 2-10– An example of motor analysis for the representative visuomotor neuron shown in previous figure. A) RF plotted in Ts Model B) RF plotted in eye displacement model (dE) which is the best fit. C) Spike density and raster plot for the motor activity. D) Statistical comparison between the models.

Figure 12B and C (with the same horizontal axis and color code as A) highlight these trends by providing frequency histograms for our different responses and neuron populations along the Te-Ge continuum. This produced a wide distribution of fits, even beyond Te and beyond Ge. This is consistent with the theory that behavior is determined by the overall balance between

members of the neuronal population, rather than individual neurons (Pouget and Snyder 2000; Blohm et al. 2009).

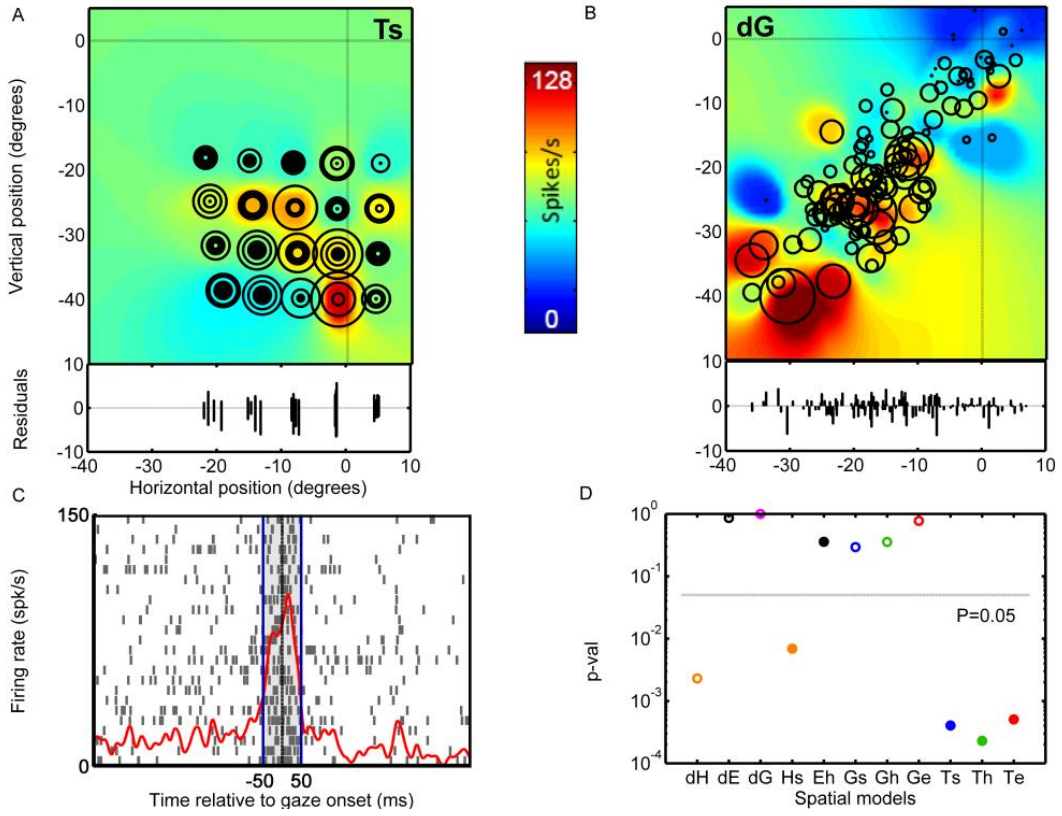

Figure 2-11– An example of analysis for a representative motor neuron. A) RF plotted in Ts model coordinates B) RF plotted in gaze displacement (dG) model which is the best fit. C) Spike density and raster plot for this motor neuron. D) Statistical comparison between the models.

However, within this distribution, both types of visual responses (i.e. by visual and visuomotor neurons) showed their major cluster around Te (Fig. 12B) whereas both types of motor response (i.e. by visuomotor and motor neurons) showed their major cluster around Ge (Fig. 12 C). In other words, along the physical continuum between target position and gaze end points, visual responses tended to code positions near to the target, and motor responses tended

to code positions near the gaze end point. Plotted this way, there was a clear and significant shift between the coding of the visual and motor responses ($P<0.0001$, unpaired t-test).

To examine whether this shift in spatial coding could occur *within* individual visuomotor neurons (which by definition show both a visual and motor burst), we plotted the target-gaze continuum values of the visual vs. motor response for each visuomotor neuron (Figure 12D). Almost all of the individual visuomotor neurons lie above the line of equality, suggesting a shift from target to gaze within these neurons. Moreover, this shift was statistically significant ($P<0.001$, paired t-test) at the level of the entire visuomotor population.

2.5 Discussion

The primary goal of this study was to determine what spatial information is encoded within temporally-defined visual and motor responses in the primate SC during head unrestrained gaze shifts. Our analysis allowed us to simultaneously compare between all of the potential candidate models that have been considered in the literature. The results showed a statistical preference for eye-centered coding of target position in the visual response vs. final gaze position coding in the motor response, even *within* visuomotor cells. Further, a subtler trend emerged across neuron sub-populations, with target coding most prominent in the vision-only cells, progressively less so in the visual and motor responses of visuomotor cells, and finally being statistically eliminated in pure motor cells. In contrast, we found no clear evidence for effector-specific coding or non-retinal frames of reference in our behavioral paradigm.

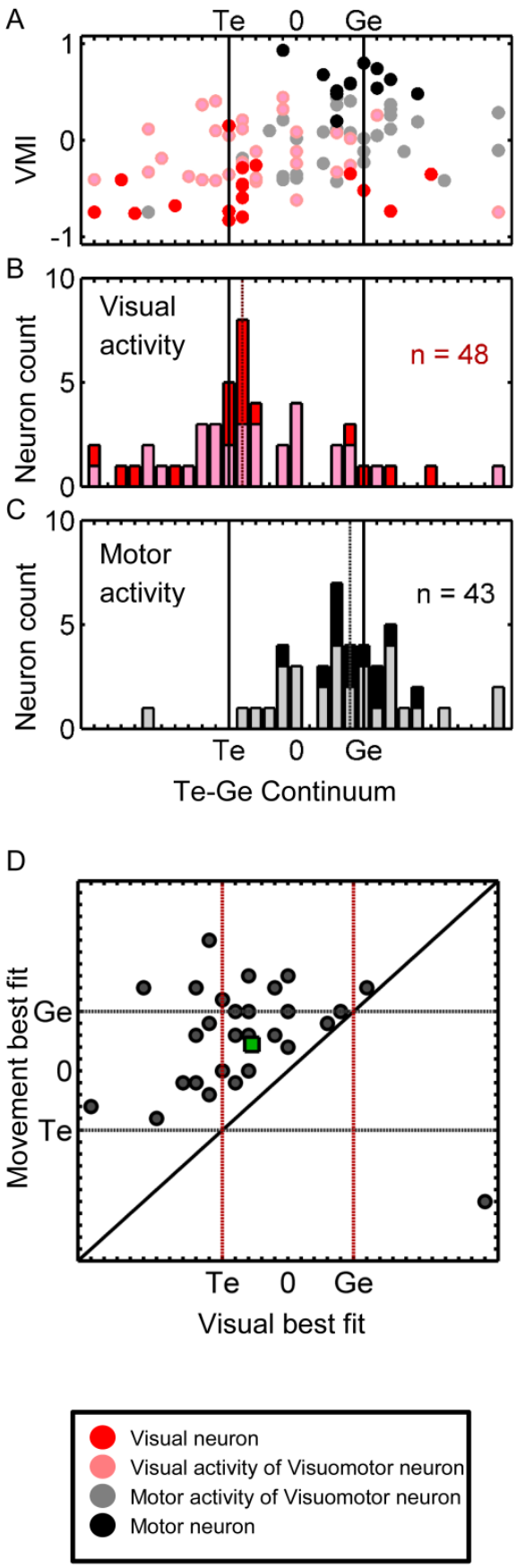
A
Te
0
Ge
1
0
-1
VMI
B
10
5
0
Neuron count
Visual
activity
n = 48
C
10
5
0
Neuron count
Motor
activity
n = 43
Te
0
Ge
Te-Ge Continuum
D
Movement best fit
Ge
0
Te
Te
0
Ge
Visual best fit
Visual neuron
Visual activity of Visuomotor neuron
Motor activity of Visuomotor neuron
Motor neuron

Figure 2-12- Population analysis of visuomotor coding along the Target-Gaze Continuum. A) Plot of visuomotor index value against target vs. gaze coding tendency (TG values) which exhibits a weak correlation (R^2= 0.092). B) Frequency distribution of target vs. gaze coding of visual activity of visual neurons (red) and visuomotor neurons (pink). Note the clustering of neurons around Te model with comparably low frequency of neurons represented at the gaze end of the continuum. The average target vs. gaze tendency of the population is represented by the dashed vertical red line. C) Frequency distribution of target vs. gaze coding for motor activity of visuomotor (grey) and motor (black) neurons. Note the clustering of neurons around the Ge model with very few representations around Te. The overall average of target vs. gaze coding of the population is represented by the vertical dashed grey line. These changes in distribution pattern between visual and motor activity and different neuron classes further suggests a visual to motor transformation between different neuron types in SC. D) The target and gaze preference of visual and motor activity of visuomotor neurons. Each neuron is represented by a black circle and the average of the population is represented by the green square. Almost all neurons lie above the equality line which is suggestive of a target-to-gaze related transformation from visual to motor activity of individual visuomotor neurons.

Visual to motor transformation

Although the SC is closely associated with visuomotor transformations (Schiller and Wurtz 1975, Sparks 1986, Sparks 1988, Gandhi and Katnani 2011, Katnani and Gandhi 2011) it remained unclear to what degree these transformations occur within the SC (Takeichi, Kaneko et al. 2007) as opposed to downstream from the SC (Klier, Wang et al. 2001, Edelman and Goldberg 2002, Klier, Wang et al. 2003). In anti-saccade experiments, visual responses are tied to the location of the visual stimulus, whereas motor responses are linked to the direction of the saccade (Everling, Bell et al. 1999, Everling, Dorris et al. 1999, Edelman and Goldberg 2001). But in anti-saccades, animals might imagine a target opposite to the stimulus (Zhang and Barash 2000, Munoz and Everling 2004, Fernandez-Ruiz, Goltz et al. 2007). Consistent with this, SC activity correlates better with target position than position-dependent errors in memory-guided saccades (Sparks

1989, Gnadt, Bracewell et al. 1991, Edelman and Goldberg 2001). Further, when targets and saccades are dissociated through weakening of the eye muscles or visual feedback training, SC activity is also linked to target location (Frens and Van Opstal 1997, Edelman and Goldberg 2002, Quessy, Quinet et al. 2010), although one study suggested that superior colliculus activity can reflect saccadic adaptation (Takeichi, Kaneko et al. 2007). These results are important, but it is not trivial to extrapolate from a perturbed system to the normal system, especially if the adaptation mechanism (e.g., the cerebellum) operates in parallel to the main sensorimotor channel (Optican and Robinson 1980, Straube, Deubel et al. 2001).

One advantage of our approach is that the visual-motor separation was accomplished simply through natural, untrained variability in gaze end points (Platt and Glimcher 1998). Previously, when we applied this method to a pooled visual and motor response across all types of SC neurons in a visually-guided gaze task (i.e., no delay to separate visual and motor activity types), target coding dominated the results (DeSouza et al. 2011). If we pooled all of the data in the current study, we would likely obtain the same results, since the Te model is so dominant in visual responses and remains a candidate model for motor responses in visuomotor neurons. However, when we separated the 'visual response' from the 'motor response', and found: 1) pure visual neurons encode the location of the target, 2) target coding is also preferred, but less distinct in the visual response of visuomotor neurons, 3) the motor response of visuomotor neurons preferentially encodes final gaze position, and 4) this preference becomes most distinct in pure motor cells, where target coding was statistically eliminated. Based on these findings, it is tempting to posit a progressive transformation between visual neurons, to a behavioral output in the pure motor neurons.

If this is true, it does not mean that these transformations are occurring exclusively within and between SC neurons. Although some SC visual cells are known to receive direct input from the retina (Sparks 1986), and SC motor responses directly influence reticular formation saccade responses (Rodgers et al. 2006, Yasui et al.1994), the intermediate connections between the superficial and deep layers of the superior colliculus involve complex pathways involving the cerebral cortex (Wurtz and Albano 1980), and the SC receives feedback from the brainstem burst generator (Moschovakis et al. 1988). Thus, this signal progression could reflect events throughout the entire saccade system. Consistent with this, in a recent study of frontal eye field activity using very similar methods, we found a similar transition from visual to motor coding (Sajad et al. 2014). However, in our superior colliculus data the visual-motor progression was more complete at the level of pure motor neurons.

Another limitation of our study that we did not establish is that which of our cells project to the brainstem gaze control generator versus feedback to the thalamus / cortex (Sommer and Wurtz 2004, Sommer and Wurtz 2004). However, these schemes do not conflict, because visuomotor and motor cells tend to provide such projections (Sommer and Wurtz 2000), and our results suggest that these cells would provide the most accurate estimate of actual gaze motion.

No previous study compared the visual activity of these various SC neuron types in terms of target vs. gaze parameter codes. Some studies have proposed that distinct subgroups of visuomotor neuron populations are involved in transferring the retinal error signal of the visual activity to downstream structures, for example the quasivisual cells (Mays and Sparks 1980) and the visually triggered movement cells (Mohler and Wurtz 1976), but these studies did not suggest a

transformation in spatial information until further downstream (Sparks 1986, Sparks 1988, Hepp, Van Opstal et al. 1993, Stanford and Sparks 1994, Sparks 2002).The current study suggests that the SC does not simply relay the retinal code; it is also involved in a transformation.

One of our most striking findings was the significant shift of coding along the target-gaze continuum between the visual and motor bursts of visuomotor cells, with this trend showing up clearly *within* almost all individual neurons. This has never been shown before in SC visuomotor cells in 'pro' saccades, but similar observations have been made using other saccade and reach paradigms in dorsal premotor cortex (Caminiti, Johnson et al. 1991, Crammond and Kalaska 2000), primary motor cortex (Ashe and Georgopoulos 1994), posterior parietal cortex (Buneo, Jarvis et al. 2002, Bremner and Andersen 2012), prefrontal cortex (Funahashi, Bruce et al. 1990), Frontal eye field (Everling and Munoz 2000), and lateral intraparietal cortex (Barash, Bracewell et al. 1991, Barash, Bracewell et al. 1991).

How and when does this transformation arise? In our memory-delay paradigm, it is possible that the visual-to-motor transformation occurs between visual and delay responses, during the delay, or in the transformation from delay activity to motor activity. This evokes the possibility that the gaze signal 'wanders away' from the target signal due to faulty recurrent feedback in the short-term memory circuit (Compte et al. 2000, Chang et al. 2012, Wimmer et al. 2014, Sajad et al. 2014). Another possibility is that the differences between visual and motor codes arise at the time of the motor burst due to feedback signals that are not present in the visual response (Soetedjo et al 2002; Matsuo et al 2004; Choi and Guitton 2006; Choi and Guitton 2009). For example, some models and evidence suggest that during gaze shifts, SC motor responses are

influenced by a brainstem feedback loop that would tend to relay highly accurate measures of the actual metrics of the gaze shift (Robinson 1973; Becker and Jurgens 1979; Everling et al. 1998; Guitton et al. 2003).

Effector specificity

A crucial aspect of gaze control is the decomposition of target position into separate commands for gaze (or the eye) versus the head (Daye et al. 2014). Unlike our previous study (DeSouza, Keith et al. 2011), here we were able to distinguish whether the motor activity of SC neurons are coding the movement vectors or final position of eye or head separately (the dE, dH, Eh and Hs respectively) as opposed to gaze models. Consistent with our frontal eye field results (Sajad et al. 2014), we found that overall, SC motor activity fits best with gaze-related models (Ge and dG) although the eye displacement model (dE) was not significantly eliminated. This was likely because eye displacement dominated the gaze shifts in our animals, so dE was very similar to the gaze displacement models. However, the dH model was significantly eliminated in all of our motor activity populations, even when we considered the full burst and head movement durations. This agrees with most previous studies which suggest that the saccade-related activity in the SC is better correlated with gaze motion than eye motion and is only poorly related to head movements alone (Freedman and Sparks 1997). It has been suggested that two-dimensional gaze displacement signals from the SC are dissociated downstream by the brainstem into separate three-dimensional eye and head control signals (Martinez-Trujillo, Klier et al. 2003, Stuphorn 2007), likely involving signals from the cerebellum and vestibular system (Van Opstal et al. 1996; Straumann et al. 2000; Glasauer et al.2003; Lehnen 2008,).

This contrasts to some studies that have found head related activity in the SC, (Walton, Bechara et al. 2007, Gandhi and Katnani 2011, Monteon, Avillac et al. 2012). However, those experiments deliberately dissociated eye and head displacement and/or used very large excursions in head position, whereas the current study employed gaze shifts from a central range. Therefore these responses may reflect other, currently unknown aspects of head movement besides its physical contribution to gaze shifts (Gandhi and Katnani 2011, Monteon, Avillac et al. 2012).

Frames of reference

For a successful visuomotor transformation, the frame of reference of sensory input (here the eye) has to ultimately be transferred into appropriate frame for muscle contraction (here eye rotation relative to the head and head rotation relative to the torso). Areas of the brain involved in sensorimotor transformations contain a complex array of signals with some areas showing intermediate frames of reference (Avillac, Deneve et al. 2005, Mullette-Gillman, Cohen et al. 2005, Mullette-Gillman, Cohen et al. 2009, Monteon, Wang et al. 2013). Nevertheless, eye-centered representations often dominate the early stages of visuomotor transformations (Buneo, Jarvis et al. 2002, Crawford, Henriques et al. 2011). This is consistent with most head-fixed studies (Andersen, Essick et al. 1985, Sparks 1989, Chen, Getchell et al. 1993, Cohen and Andersen 2002) and extends to head-unrestrained studies of the SC (Klier, Wang et al. 2001, DeSouza, Keith et al. 2011).

In the current SC study –much like our recent frontal eye field study (Sajad et al. 2014) — gaze-centered representations again predominated, i.e., Te and Ge were the two most common best fits across all visual and motor responses, followed by dG. Te clearly dominated the visual

response, but we could not separate the Ge (final gaze position relative to eye) and dG (Gaze displacement; which is the same as the projection of final gaze position relative to the fixation point on screen) models in our motor responses. Both are gaze-centered, in the sense that initial gaze direction is the '0' in this coordinate system, but the coordinate axes for dG are actually fixed in space whereas the coordinate axes of Ge are fixed in the eye (Crawford and Guitton 1997). This necessitates a 3-D position-transformation between Ge and dG (Blohm and Lefevre 2010). Our data suggest that such a transformation could occur between visuomotor neurons (which fit Ge best) and motor neurons (which fit dG best), but the population analysis for these models were nearly identical and certainly not statistically different. This is probably because these two models are geometrically very similar up to gaze excursions of 30º, which encompasses most of the data recorded here (Crawford and Guitton 1997). A previous stimulation study was able to separate these models by evoking very large gaze shifts from the SC, and here, the Ge model was clearly preferred (Klier, Wang et al. 2001). The most parsimonious explanation is that the motor output of the SC encodes Ge, but it is possible that the SC is able to transform Te signals (whether from visual input or from electrical stimulation) into a dG output in its motor response as a function of intrinsic gaze position signals (Van Opstal et al. 1995; Smith and Crawford 2005; DeSouza et al. 2011). Testing between these options will require further experiments that focus on very large gaze shifts and/or gaze shifts from large torsional offsets in eye positions.

Timing Determines Tuning: a Rapid Spatiotemporal Transformation in Superior Colliculus Neurons During Reactive Gaze Shifts.

Morteza Sadeh, Amirsaman Sajad,2, Hongying Wang, Xiaogang Yan and John Douglas Crawford

(Manuscript submitted to Journal of Neuroscience)

3.1 Abstract

Abstract

Gaze saccades –rapid shifts of the eyes and head toward a goal— have provided fundamental insights into the neural control of movement. For example, it has been shown that the superior colliculus (SC) transforms a visual target (T) code to future gaze (G) location commands after a memory delay. However, this transformation has not been observed in 'reactive' saccades made directly to a stimulus, so its contribution to normal gaze behavior is unclear. Here, we tested this using a quantitative measure of the spatial continuum between T and G coding based on variable gaze errors. We demonstrate that a rapid T-G transformation occurs between SC visual and motor responses during reactive saccades, even *within* visuomotor cells, with a continuous spatiotemporal shift in coding occurring in cell types (visual, visuomotor, motor). We further show that the primary determinant of this spatial code was not the intrinsic visual-motor index of different cells or populations, but rather the *timing* of the response in *all* cells. These results suggest that the SC provides a rapid spatiotemporal transformation for normal gaze saccades, that its motor responses contribute to variable gaze errors, and that those errors arise from a noisy spatiotemporal transformation involving all SC neurons.

Significance Statement

Oculomotor studies have demonstrated visuomotor transformations in structures like the superior colliculus with the use of trained behavioral manipulations, like the memory delay and antisaccades tasks, but it is not known how this happens during normal saccades. Here, using a spatiotemporal model fitting method based on endogenous gaze errors in 'reactive' gaze

saccades, we show that the superior colliculus provides a rapid spatiotemporal transformation from target to gaze coding that involves visual, visuomotor, and motor neurons. This technique demonstrates that SC spatial codes are not fixed, and may provide a quantitative biomarker for assessing the health of sensorimotor transformations.

3.2 Introduction

Saccades and rapid gaze shifts involving coordinated eye-head motion have been employed extensively to study the fundamental neural basis of sensorimotor transformations (Mays and Sparks 1980, Wurtz and Albano 1980, Gnadt, Bracewell et al. 1991, Deubel 1995, Freedman and Sparks 1997, Freedman and Sparks 1997, Freedman 2008, Sadeh et al. 2015, Sajad et al. 2015). As a result, the circuitry of the saccades system in humans is very well described (Fischer 1986, Pierrot-Deseilligny et al. 1991, Pierrot-Deseilligny, Rivaud et al. 1991, Gaymard and Pierrot-Deseilligny 1999, Munoz and Everling 2004). Studies in non-human primates have revealed numerous additional details about the cellular and signal properties. For example, neurons with gaze-related responses in the superior colliculus (SC), frontal eye fields, (FEF) and lateral intraparietal cortex (LIP) can be categorized into populations of cells with 'visual' responses (briefly delayed burst responses to a visual stimulus), 'motor' responses (burst activity just before and after a saccade) or visuomotor responses, i.e., both visual and motor (Goldberg and Wurtz 1972, Goldberg and Wurtz 1972, Harris 1980, Goldberg and Bushnell 1981, Bruce and Goldberg 1985, Bruce, Goldberg et al. 1985, Munoz and Wurtz 1995, Munoz and Wurtz 1995, Freedman and Sparks 1997, Bisley and Goldberg 2003, Gandhi and Katnani 2011). The timing of these

responses seems to imply a spatiotemporal transformation between the visual and motor responses, but demonstrating this transformation in the spatial domain is not trivial.

Normally there is little or no temporal separation between visual and motor responses, and little separation between the direction of a visual stimulus and saccade direction, so visual and motor responses are easily conflated in both the temporal and spatial domains. The technical challenge for spatial separation is that the key parameters –retinal location of a visual target and gaze displacement— only diverge in the presence of saccade errors (Mays and Sparks 1980, Waitzman, Ma et al. 1988, Stanford and Sparks 1994, Munoz and Everling 2004), ocular torsion (Crawford and Guitton 1997, Klier and Crawford 2003), or very large gaze shifts (Klier, Henriques et al. 2002). Studies of this question have mainly used saccade errors and focused on structures such as the midbrain superior colliculus (SC) and cortical areas like the frontal eye fields (FEF), and lateral intraparietal cortex (LIP). In general, many experiments suggest that these structures employ a retinal spatial code (Klier, Wang et al. 2001, Martinez-Trujillo, Medendorp et al. 2004, Avillac, Deneve et al. 2005, Constantin, Wang et al. 2007, DeSouza, Keith et al. 2011, Monteon, Wang et al. 2013, Sadeh, Sajad et al. 2015, Sajad, Sadeh et al. 2015), although some have suggested they encode displacement of gaze direction (Mays and Sparks 1980, Freedman and Sparks 1997, Horwitz and Newsome 1999, Knight and Fuchs 2007, Marino, Rodgers et al. 2008). A use of a purely retinal code would seem to suggest that the conversion into motor coordinates only happens further downstream, in structures such as the brainstem reticular formation (Sparks 1989, Sparks and Hartwich-Young 1989, Snyder 2000, Sparks 2002, Crawford, Henriques et al. 2011, Sadeh, Sajad et al. 2015).

The challenge for detecting a spatiotemporal transformation is even higher, because it requires distinguishing retinal and motor codes within the short time span of the neural response to a single saccade target. One useful technique is to train animals to saccade opposite to the target (the anti-saccade task), using a spatial dissociation between target position and gaze direction. This has shown that many cells in the SC, FEF, and LIP initially encode visual target direction, but then switch to coding saccade direction (Gnadt, Bracewell et al. 1991, Groh and Sparks 1992, Optican 1995, Gottlieb and Goldberg 1999, Russo and Bruce 2000, Marino, Rodgers et al. 2008,). Another approach is to separate visual and motor responses in time, through the interposition of a memory delay, and then fit various models against the response to targets at various directions in the presence of small, variable saccade errors. This showed that the SC and FEF visual response encodes target location (T) relative to the eye, whereas the motor response encodes future gaze direction (G) relative to the eye (Sadeh, Sajad et al. 2015, Sajad, Sadeh et al. 2015). A further spatiotemporal analysis of these results showed that the T-G transformation occurred continuously through intermediate codes during the memory delay, and then shifted to G in purely motor cells active just before a saccade (Sajad, Sadeh et al. 2016).

These findings, while important, employ experimental manipulations of behavior that are not normally present in saccades. For example, we do not normally look away from stimuli; this requires suppression signals and might cause the brain to imagine a target in the opposite direction (Bell, Everling et al. 2000, Everling and Munoz 2000, Munoz and Everling 2004, Coe and Munoz 2017). Likewise, we do not always delay saccades, and this task introduces suppression signals, memory signals, and a memory-motor transformation. These might introduce the accumulation of internal errors that artificially create an apparent 'transformation' (Gnadt,

Bracewell et al. 1991, Stanford and Sparks 1994, White, Sparks et al. 1994, Ohbayashi, Ohki et al. 2003, Barber, Caffo et al. 2013, Hollingworth 2015, Sadeh, Sajad et al. 2015, Sajad, Sadeh et al. 2015, Sajad, Sadeh et al. 2016). Thus, it is not trivial to transpose these results to simply 'reactive' saccades made immediate and directly to a transient stimulus. It is simply not known whether a spatiotemporal transformation occurs during reactive saccades, and if so, how different SC cell types contribute to this transformation.

In the current study we directly investigated if the continuous neural activity present during reactive saccades shows the same spatial transformation that has been shown in the memory delay paradigm. To do this, we recorded from the same SC neurons using both the reactive and memory delay tasks, and analyzed their spatial content using a model fitting approach that we have developed and used recently (Keith and Crawford 2008, DeSouza, Keith et al. 2011, Sadeh, Sajad et al. 2015, Sajad, Sadeh et al. 2015). Further, we used a variant of our recent spatiotemporal analysis (Sajad, Sadeh et al. 2016) to test for a rapid transformation within the continuous burst present during reactive saccades. We found that, in the absence of a memory delay, SC neurons produce a rapid spatiotemporal transformation from retinal to gaze coding through a distributed transformation that appears to depend more on timing than cell type.

3.3 Methods

Animals and Surgical Procedures

The data were collected from two female monkeys (Macaca Mulatta, M1 and M2; age, 10 years; weights, 6.5 and 7 kg) with a protocol approved by the York University Animal Care Committee in accordance with guidelines published by the Canadian Council for Animal Care. With similar

surgical procedures as described previously (Crawford, Ceylan et al. 1999, Klier, Wang et al. 2001), the monkeys were prepared for long-term electrophysiology and 3D gaze movement recordings. Each monkey was subjected to general anesthesia with 1–2% isoflurane after intramuscular injection of ketamine hydrochloride (10 mg/kg), atropine sulphate (0.05 mg/kg), and acepromazine (0.5 mg/kg). In order to minimize the collisions between experimental setup and Microdrive/electrode we implanted a vertically aligned unit recording chamber (i.e. with no tilt) placed 5 mm anterior and 0 mm lateral in stereotaxic coordinates, which allowed access to the left and right SC. This chamber angle and position were chosen to minimize collisions between the electrode/microdrive and the experimental setup during head movements, and to simplify the use of stereotaxic coordinates during recordings. The chamber was then surrounded by a dental acrylic cap, which was anchored to the skull with 13 stainless steel cortex screws. Two scleral search coils (diameter, 5 mm) were implanted in one eye of the monkeys to record 3D eye movements. Two orthogonal coils, which were secured with a screw on a plastic base on the cap, recorded the 3D head movements during the experiments. 3D recordings and analysis were performed as described previously (Crawford, Ceylan et al. 1999, DeSouza, Keith et al. 2011).

Experimental equipment

We used a Pentium IV PC and custom-designed software to present stimuli, control behavior paradigms, send digital codes to a Plexon data acquisition system, and deliver juice rewards to the monkeys. Stimuli were presented on a screen 60 cm in front of the monkey, by use of a projector (WT600 DLP projector; NEC). Monkeys were seated on a custom-designed primate chair to have their heads move freely at the centre of a 1-m3 magnetic field generator (Crawford

et al., 1999), and a juice spout (Crist Instruments) was placed on the skull cap for computer-controlled delivery of the juice reward to the monkey's mouth.

Behavioural recordings and paradigms

All experiments were performed in head-unrestrained conditions. This was necessary for the preliminary general reference frame analysis that preceded this experiment (Sadeh, Sajad et al. 2015). Here, target (T) and gaze (G) position in eye coordinates were the key parameters, but head unrestrained recordings also had advantages here: comfort, natural system behavior, adequate range of gaze motion for testing large neural response fields (RF; see below), and the tendency toward more prolonged neural activity for a spatiotemporal analysis (Keith, DeSouza et al. 2009, DeSouza, Keith et al. 2011). Conversely, 3D recordings and analysis were required for the proper transformation of T and G data to eye coordinates, to account for the significant torsional eye rotation and prominent non-linearities that occur in the head unrestrained gaze range (Tweed and Vilis 1987, Crawford, Ceylan et al. 1999, Klier, Wang et al. 2003, DeSouza, Keith et al. 2011).

The primary behavioral condition used during our neural recordings was the *Reactive* gaze shift task (Figure 1). The spatial aspects of this task were optimized for the model fitting analysis described below, including the separation of different reference frames and more importantly here, T from G coding. Animals were trained to begin each trial by fixating a central position (green circle with radius of 0.5°), with a location that randomly varied within a predetermined square range approximately equal to the cell's RF size - for 900-1000 ms (randomly varied interval); simultaneous with initial fixation point disappearance-serving as GO signal - a target

(red circle with a size of 0.5°) was presented in the periphery for 125 ms, brief enough to ensure no visual feedback after the completion of the gaze shift.

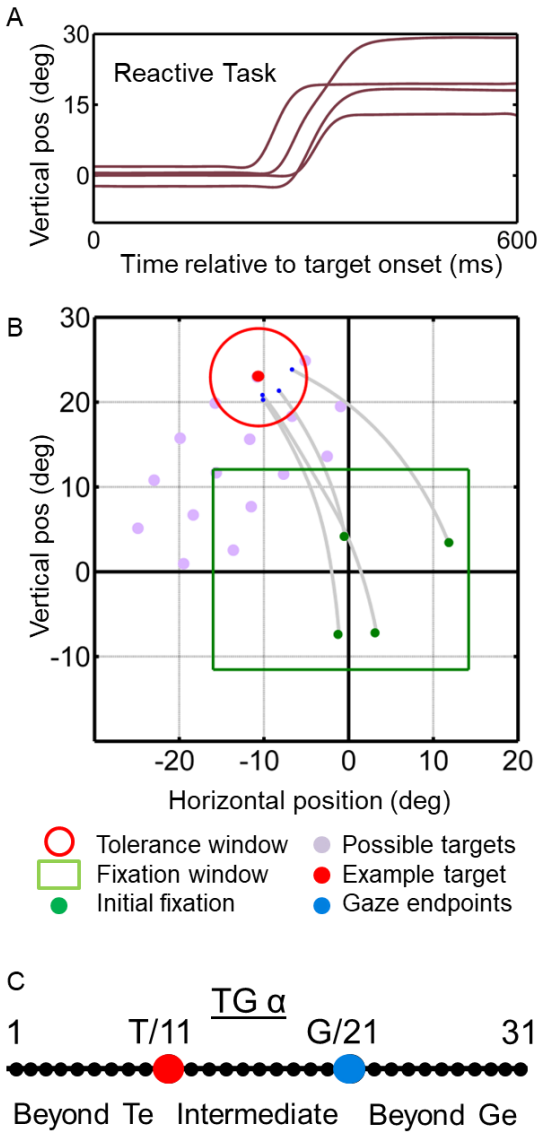

Figure 1: A) example traces of vertical eye position plotted as a function of time. B) Two-dimensional gaze trajectories (grey lines) from the *reactive task* for an example target in monkey M2. Also shown are the range of initial fixation positions (green square), the tolerance window (red circle), and the other possible targets used in this experimental session (grey circles) to map a neuron's receptive field. C) The schematic illustrating the target gaze continuum concept, the distance between and beyond the target location and gaze are divided into 31 points and the fit to neural activity is perform at each of the discrete locations to identify the best fit.

The location was previously determined from preliminary RF mapping. Animals were then required to make a gaze shift toward the briefly flashing stimulus and fixate on it for 200 ms in order to receive juice reward. To spatially separate targets from gaze coding, we designated a tolerance window of 6–12° (diameter) for gaze errors around the locations of the targets, which

resulted in a naturally-generated distribution of gaze end points around the targets (See Figure 1A, B, C). This variable error is the basis of our analysis method (Sajad, Sadeh et al. 2015).

In addition, we recorded the same neurons in a *Memory delay* task (Sadeh, Sajad et al. 2015). This was identical to the reactive task, except with a memory delay of 400-700ms during which the animal had to maintain fixation before making a saccade. These results were analyzed previously (Sadeh, Sajad et al. 2015) and are only used here to distinguish different neuron types. A more detailed description of eye-head kinematics in this task was described previously (Sadeh et al. 2015); here we focused on gaze kinematics relative to target location.

Trial definition and inclusion criteria

The beginning of a trial was marked by the appearance of the initial fixation point. The beginning of the gaze saccade was defined as the instant when its velocity exceeded 50°/s, and its end when its velocity decreased to 30°/s. The contribution of the head movement to gaze is defined here as the head movement from the start to the end of the gaze saccade. However, the head movement was often prolonged after the saccadic component of the gaze shift. Head movements were marked from the start of gaze movement until the point at which the head velocity decreased to below 15°/s. The head movement marks were then visually inspected to ensure correct marks. All trials were considered for analysis irrespective of whether or not the monkey received a reward after the trial. We excluded trials on the basis of spatial and temporal criteria. First, trials in which the directions of the gaze shifts were completely unrelated to the direction of the target (e.g. opposite direction) were removed. Then, we obtained the regression between errors in gaze vs. retinal error (the retinal angle between the fovea and the target at the initial

eye position before the gaze shift), and removed trials with gaze error two standard deviations greater than this regression line. Furthermore, every trial was visually inspected, and any trial in which the gaze shift was anticipated (reaction time of < 100 ms after the go signal) and when the gaze shift consisted of multistep saccades was excluded. Finally, for each neuron, we required successful performance for at least 80% of total trials [mean standard error of the mean (SEM) trials = 178(16)], and at least seven successful gaze shifts towards each target location (with a possible maximum of 15, after excluding erroneous trials); also, the neuron had to remain isolated throughout the recording session.

Neural recordings

We recorded extracellular activity from the left and right SC with tungsten microelectrodes (FHC). The electrode was inserted through a guide tube, which was controlled by a hydraulic microdrive (MO- 90S; Narishige International, East Meadow, NY, USA). Isolated signals were amplified, filtered and stored for off-line sorting with the Plexon MAP system. The SC was identified according to criteria published previously (DeSouza, Keith et al. 2011, Sadeh, Sajad et al. 2015). The steps of SC identification and confirmation are identical to those explained previously (Sadeh, Sajad et al. 2015). The memory delay saccade task was used to dissociate between visual and movement related activities and categorize cells into visual, visuomotor (VM) and motor neurons. Visual neurons were defined as cells that showed a robust burst of activity (> 50 spikes/s above the baseline) 40– 60 ms after the stimulus presentation that lasted for ~180 ms afterwards (Goldberg and Wurtz 1972). Motor neurons were those with robust activity or a buildup of activity peaking at the time of gaze onset, with activity starting prior to the gaze onset (100–40

ms before saccade), and that continued to ~100 ms after gaze onset. Neurons that met both criteria were classified as visuomotor. We also used a visuomotor index (VMI = (Motor spike count - Visual spike count / (motor spike count + visual spike count) to quantatively separate these based on our previously published memory-delay task data (Sadeh, Sajad et al. 2015). The visual and motor burst spike counts were first subtracted from the baseline activity (100ms pre-target period). This gave a score where -1 is a purely visual neuron and +1 a purely motor neuron). Neurons classified as visual had VMI values ranging from -0.83 to 0.42, visuomotor neurons ranged from -0.74 to 0.51 and the pure motor neurons had VMI values from -0.2 to 0.74. When we refer to 'number of spikes' below, this refers to number of action potentials in these defined temporal windows, also we use neural activity and burst interchangeably to refer to the same concept of high frequency of action potentials.

The temporal windows that we used for analysis of bursting activity in the reactive task are illustrated in the results section (Figure 2). For some analyses (i.e., Figures 3,4) we used a fixed window of +70 to +170ms relative to visual target presentation for visual activity (shown as red vertical lines) and -50 to +50 ms relative to saccade onset (shown as black vertical lines). For other analyses (i.e. Fig. 5, 6) we considered the entire burst duration of the neurons (windows shown as blue vertical lines). The average range of the entire population burst (aligned on stimulus presentation) was 342 ms. For visual neurons the full duration of burst was defined as the time which the activity increases above 50 spikes/s after the stimulus presentation to a point detected by visual inspection at which the activity considerably declines, this window was on average from +48 ms (start) to +231 ms (end) relative to visual stimulus onset. For VM neurons the average range of the entire burst was +47ms to +421 ms relative to visual stimulus onset. For motor

neurons the average range was -94 to 194 ms relative to saccade onset. Finally, for figures 6 and 7, we performed a step wise analysis of the entire duration of individual neuron activities broken down into smaller time windows in order to investigate changes in spatial coding during the neural activity (see 'spatiotemporal analysis' approach below).

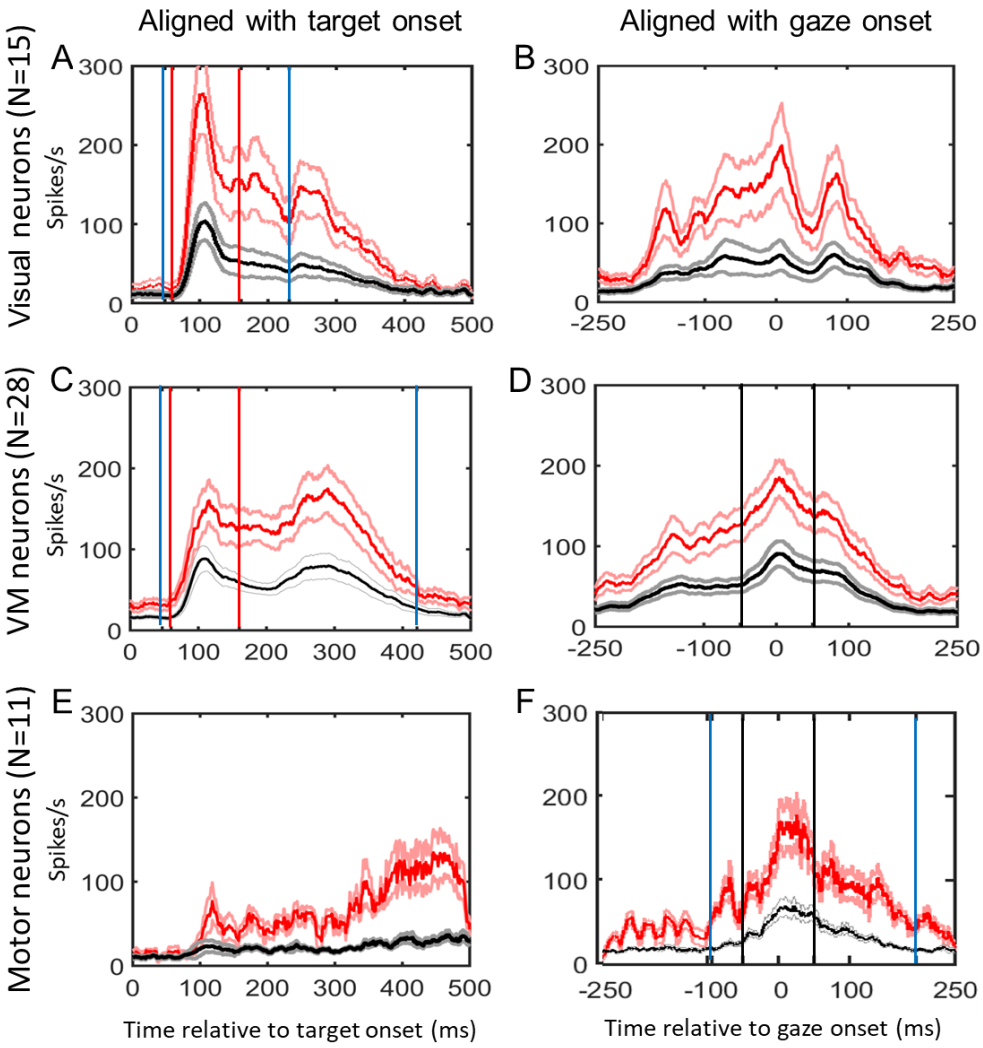

Figure 2: Mean spike density plots, averaged across our three populations of neurons in the reactive task, showing all data that passed our exclusion criteria. Data aligned with stimulus onset (*left column*) and gaze movement (*right column*). red lines were derived from the 'top 10%' trials in the reactive task (±SEM, light red lines), and the black lines are derived from the average firing rate across all trials (±SEM, grey lines). Solid blue vertical lines indicate the average temporal analysis window for the 'full burst' analysis, whereas red and black vertical lines indicate the time

intervals sued for the 'fixed window' analysis in visual and motor activities respectively. A and B) the visual neurons (N=15); C and D) Visuomotor neurons (N=28); E and F) Motor neurons (N=11), identified using the *memory delay task* (Sadeh et al. 2016).

Spatial Analysis of Neuronal Response Fields

Visual and motor RFs were obtained for each neuron for all of the models and in order to analyze and compare the spatial coding we used several spatial models to fit the RF data for each neuron using a method that has previously been described several times (Keith, DeSouza et al. 2009, DeSouza, Keith et al. 2011, Sadeh, Sajad et al. 2015, Sajad, Sadeh et al. 2015). Briefly, the RF of the neuron was plotted by overlapping firing rate data over two-dimensional position data corresponding to the spatial parameter related to the given model (e.g., final gaze position relative to the eye; for the list of models tested in this study see below). Spatial models were then constructed by fitting the RF data non-parametrically using Gaussian kernels with bandwidths ranging from 2-15 degrees. The qualities of the model fits were quantified by calculating the Predicted Sum of Squares (PRESS) residuals for all trials, which is a type of cross validation in regression analysis (Keith, DeSouza et al. 2009). The spatial code of a neuron was then defined as the model (at the kernel bandwidth) that yielded the overall best fit (i.e. smallest residual) to the data. Briefly, PRESS residual for every trial was obtained by: 1) eliminating that trial from RF data, 2) fitting the remaining data points non-parametrically using Gaussian kernels at various bandwidths (2-15°), and 3) obtaining the residual between the fit and the missing data point. The overall predictability power of the model for the recorded data set was quantified by the average of PRESS residuals across all trials for that neuron.

As noted above, the spatial parameters in our behavioral task (Figure 1) were designed to distinguish between various frames of reference using the analysis described above. These were tested exhaustively in a previous analysis of neurons recorded in the memory delay paradigm (Sadeh, Sajad et al. 2015); (which used an overlapping but larger population of neurons) we tested eleven models that have been proposed for spatial coding in the eye and head movement control system against the visual and movement responses of all neurons. This included models of target location vs. gaze, eye-in-head, and head motion (both final position and displacement) in eye-centered, head-centered, and body-centered frames of reference). This yielded an overall preference of SC neurons for target (T) and gaze (G) position codes described in eye-centered coordinates. These results allowed us to narrow down and refine our spatial models to examine neuronal coding along a continuum of intermediate spatial models spanning T and G.

The physical basis of the TG continuum is illustrated in Figure 1 C, which shows the TG continuum for an example trial. This continuum extends between, and beyond T and G position for every such trial. The intermediate spatial models were constructed by dividing the distance between target position and final gaze position for each trial into 10 equal intervals and 10 additional intervals extended on either end. The location of the best-fit model along the T-G continuum (here referred to as TG alpha value) is indicated by a value between 1 to 31 (the Target and Gaze locations are arbitrarily numbered 11 and 21 respectively) indicating their relative preference for coding target vs. gaze related spatial information. For example, if the fit and TG continuum analysis for the activity of a given neuron yields the value of 20 (one step away from 21 – i.e., G), this indicates that the spatial information encoded by this neuron's activity is best described by a position between target position and gaze endpoint that's 90% described by gaze endpoint,

and only 10% by target position. Noteworthy that this analysis is not influenced by systematic errors in behaviour and entirely relies on variability in the spatial relationship between positions in different models. Once the optimal TG value is determined, it can then be used to plot neural RF's in their intrinsic coordinate system, simply by plotting activity for trial according to its location along the TG continuum (in eye-centered coordinates).

Spatiotemporal Analysis

In order to track changes in the spatial code through time (Figs 6,7), we used a step by step analysis of the entire duration of the burst when broken down into smaller time windows, i.e. analyzing each time window separately using the same model fitting approach. The specifics of the analysis approach were explained in detail previously (Sajad, Sadeh et al. 2016), but briefly: the similar spatial analysis as described above was applied to each of the time windows spanning the visual and motor neural activities and in order to account for variabilities in duration of the activities from one neuron to another without losing any of the activity in analysis we normalized the time between the onset of modulation aligned on target onset based on spike density function (mean = 57 ms after target onset for V and VM neurons, and 86 ms for motor neurons) and the time of gaze movement onset which varied on a trial by trial basis for all trials, the duration between this early visual period and gaze movement onset was on average 231 ms (± 74 ms, SD) across all trials. The normalization served to account for time and space similarly since the T-G continuum data are also obtained by dividing the spatial difference between target position and final gaze position (i.e., inaccuracy errors in behaviour) in fixed number of discrete steps on a trial by trial basis The analysis on the RF sampled from the activity within the time-

normalized windows allows for the visual and motor activities to be analyzed as a continuum to detect possible gradual changes in spatial coding through time.

The firing rate of the neuron in the corresponding window (spikes/sec; number of spikes divided by the sampling interval for each trial) was sampled at 7 semi-overlapping windows from this time-normalized data. This choice of sampling window numbers was based on the approximate ratio of the duration of the visual response to decrease in the peak and then to the start of movement response including a post-saccadic period starting from gaze onset. The final (7th) time-step corresponded to mostly post-saccadic period starting from the onset of gaze shift. Because of the time-normalization process the sampling window width scaled with the duration between visual response onset and movement onset on a trial-by-trial basis. On the 7-step time-normalized scale, the visual burst on average lasted 4 steps (SD = 0.63 steps), ending by the end of the fourth time-step in 91.2 % of trials. The sampling window width was on average 75ms (±8ms, SD) and was no less than 47ms for any trial which ensured enough neuronal spikes captured in the sampling window to perform effective spatial analysis. The time for which the first window starts was also confirmed by visual inspection of activity raster of all neurons to identify the visual bursts, movement bursts and the peaks.

Confirmation of significant spatial tuning (in neuron populations)

Since the results of our analysis approach are only considered valid if the sampled neural activity exhibits spatial tuning, we excluded any data point which did not exhibit significant spatial tuning. In order to achieve this, we used an approached described in details before (Sajad, Sadeh et al.

2016) randomly shuffled the neural activity data and plotted the data over the positional data of the best fit model for the neuron to obtain a 'random' RF. This process was repeated 100 times and therefore 100 random RFs were obtained. To do this, we randomly shuffled the firing rate data (number of spikes divided by duration of the sampling window) and plotted them over the position data corresponding to the best-fit model, and repeated this procedure 100 times to obtain 100 *random* RFs. The PRESS residuals of these random RFs (and their respective mean PRESS values) were then obtained after fitting the data (non-parametrically, using Gaussian kernels) with the same kernel bandwidth that was used to fit the best-fit model, resulting in a total of 100 mean PRESS residuals. If the mean PRESS residuals for the best-fit model ($PRESS_{best\text{-}fit}$) were at least 2SD smaller than the mean of the distribution of random mean PRESS residuals, then the sampled activity was categorized as spatially-selective. Moreover, in order to exclude any non-spatially tuned activity and reduce the overall noise to signal ratio in our population we excluded population data belonging to time-windows at which the mean spatial coherence of the population was not significantly higher from that of the baseline activity prior to target presentation which demonstrates no spatial tuning. We used a coherence index ($1 - (PRESS_{best\text{-}fit} / PRESS_{random})$) value in order to determine the contribution of each neuron to the overall spatial coherence of the population (Sajad, Sadeh et al. 2016).

3-5 Results

General Observations

We sampled 86 SC neurons during head unrestrained gaze shifts. Of these 86, we were able to record a complete data set from 74 neurons, spanning both sides of the SC in each animal. Of

these 74 neurons, 54 met all of our inclusion criteria, including 15 visual, 28 VM and 11 motor neurons (as Identified using the memory delay task; (Sadeh, Sajad et al. 2015)).

Figure 2 shows the activity profiles of each category of neurons (Visual, VM, Motor) during reactive gaze saccades to the top 10% RF 'hot spot' (i.e. the region of the RF with the highest neural activity) data (red traces) and the full RF dataset (black traces). Each panel provides mean spike density plots (averaged across neurons ± SEM). Data are aligned both with target onset (Left column; Fig 2 A, C and E) and when aligned with gaze onset (Right Column, Fig 2B, D and F). Vertical red and black lines indicate the 'fixed-window' visual and motor analysis windows respectively, whereas blue vertical lines indicate the average duration of the 'full burst analysis'. (Note that Figure 2 shows average full burst durations for neuron populations; some neurons burst for shorter or longer durations but sum over the whole range, so the mean population spike density plots show a longer duration than the mean full burst windows).

By definition, visual neurons showed a much stronger target-aligned response than saccade-aligned response (Fig. 2 A vs. B), VM cells showed approximately equal responses (Fig. 3 C vs. D), and motor neurons showed much stronger saccade-aligned responses (Fig. 3 E vs. F).

The visual neuron population showed a strong initial peak of activity 48 ± 11 ms (mean ± SD) after the stimulus onset, followed by a smaller secondary peak of activity at 210 ± 15 SD ms (Figure 2 A). The large third peak 300 ms past stimulus onset was likely residual motor activity (i.e., not excluded by our *memory saccade*-based population criteria) because it was absent in the memory delay task visual response (Sadeh, Sajad et al. 2015), and aligned closely with saccade onset

(Figure 2 C). This was excluded from the visual full burst analysis, except in the stepwise temporal analysis shown below (Figs. 6,7).

The VM population showed a first peak 106±9 ms after the visual stimulus onset (Figure 3-2B) and a second peak 9±3 ms after saccade onset (Figure 2D), separated by a short period (average 95 ± 12 SD ms) of sustained activity. Motor neurons showed a single peak of activity 22 ± 6 ms) after saccade onset (Figure 2F). Henceforth we will refer to the data from our fixed target and fixed saccade-related windows as 'visual activity' and 'motor activity', based on their temporal profiles, but use our TG- continuum analysis method to quantify what spatial parameters these activities actually encode in different neurons and at different times.

Spatial Transformation between Visual and Motor Responses

In our previous papers (Sadeh, Sajad et al. 2015) we used fixed visual and motor window analysis in combination with a memory delay paradigm to show that SC and FEF visual responses tend to code Te whereas the motor responses, following a brief memory period, tends to code Ge. The spatiotemporal analysis described above suggests that the same is true during reactive saccades, i.e., even in the absence of a memory delay. To test this directly, we repeated a fixed visual/motor window analysis on the reactive task data (see Methods and Figure 2). Note that these two temporal windows were each 100 ms in duration, and on average were shifted from each other (start-to-start) by 192 ± 23 ms, meaning that they were separated end-to-start by only 92 ± 23 ms. Thus, we were testing if a significant spatial transformation from T toward G coding occurred over a very short period of time.

Figure 3 provides example rasters and fixed analysis windows (left column) and RF fits (middle column) for a typical visual cell (top row; A, B) and motor cell (bottom row; C, D). The right column provides frequency histograms and scatter plots that contrast the TG alpha values for visual and motor window fits for our entire population of cells. The results of the visual window analysis are shown in Fig 3C. Overall, this yields a mean (12.2) and median (12) and distribution (SD 4.2) that clearly clustered near Te (11). There was no significant difference between the mean of the means of TG alpha values for the visual population (red bars) and the visual response of the VM neurons within the same time window (pink bars) (p= 0.8738, unpaired t-test). In contrast, our analysis of motor activity (Fig. 3 B) yielded an overall mean (17.3), median (18), and distribution (SD 4.7) that was shifted toward the Ge model. Again, there was no significant difference between the distribution of the motor neuron responses (black bars) versus the motor response of VM neurons (gray) within the same time window; (unpaired t-test, p=0.85. More importantly, there was a significant difference between the distributions of the visual (Fig 3A) and motor (Fig. 3B) responses (P= 0.0001, unpaired t-test)

Remarkably, this rapid shift in coding can be observed even *within* VM neurons, such as the example neuron with raster / spike density plot shown in Figure 4 A, visual receptive field in Figure 4 B, and motor response field 4 C. To directly quantify if a TG shift occurs *within* VM neurons, we plotted the TG alpha value from the motor window as a function of the value of the visual window for each neuron (Fig. 4 C). Neurons with data points that lie above the diagonal line indicate a different preference of spatial coding in their visual versus movement related activities. The mean of TG values for VM neurons is also indicated by a red circle in Figure 4D which shows that as a population there is a shift from target to gaze coding when going from

visual to movement related activities in the VM neurons. Overall, the motor TG values for VM neurons were significantly different from their visual TG values (Paired t test, p= 0.0001). Thus, a rapid transformation along the TG continuum occurred between visual and motor responses, even within VM neurons.

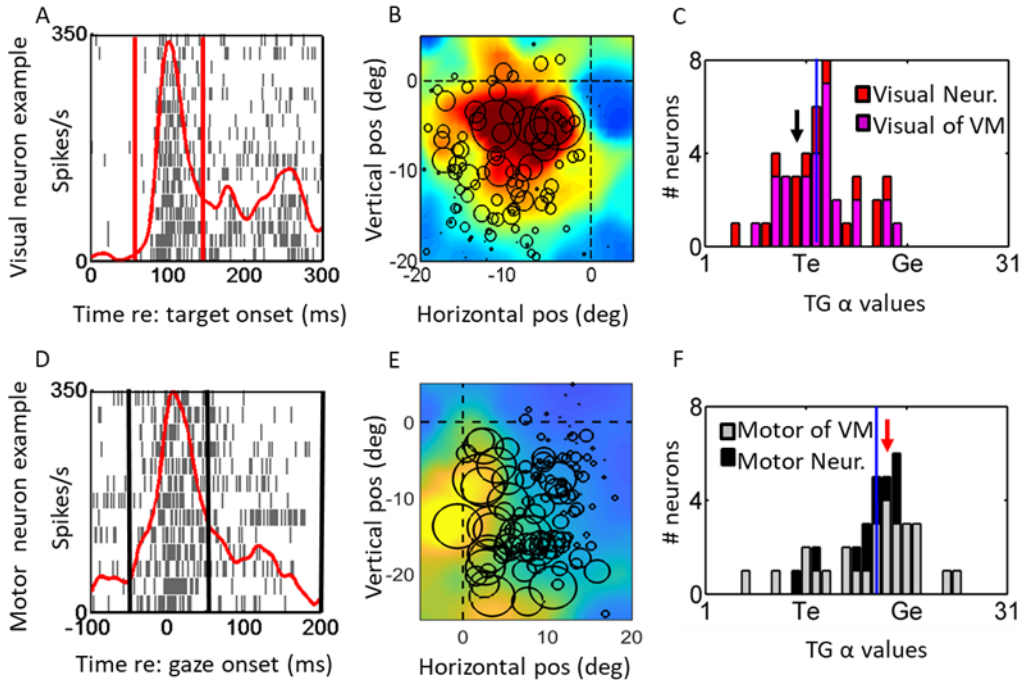

Figure 3: Shift of spatial representation from near Te in the target-aligned window analysis toward Ge in saccade-aligned window analysis of *reactive task* data. A) As representative visual neuron activity raster and B) RF plots C) The distribution of TG alpha values of visual (red bars) and visual activity of VM neurons (pink bars) when only the fixed window of visual activity is considered in the analysis, the cluster of distribution is closer to the target side if the continuum, the black vertical line represents the median of TG alpha values of visual activity of the entire visual population (both visual and VM neurons). The location of TG value for the representative example is indicated by the red arrow D) A representative Motor neuron activity raster and B) RF plot. E) The TG alpha value distribution for the motor activity of VM neurons (grey bars) and motor neurons (black bars), otherwise like A. The cluster of the distribution is closer to Ge. The location of TG value for the representative example is indicated by the red arrow. Note that the shift from the mean TG values in the visual activity histogram (C) (mean= 12.2) is significantly different (unpaired two tailed t-test, p=0.0001) from the mean in the motor activity TG histogram (F) mean (= 17.4)

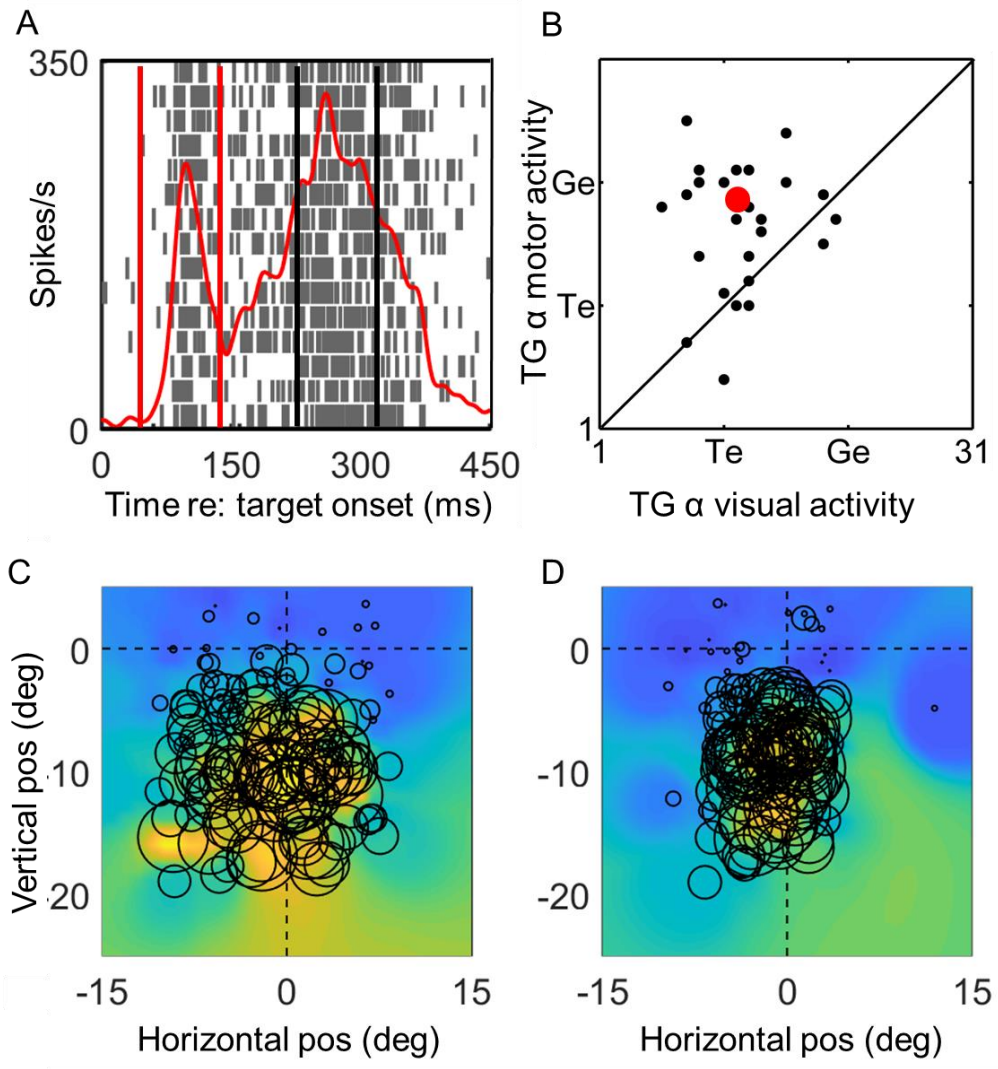

Figure 4: Shift from Te to Ge coding *within* VM Neurons. A) Raster/ spike density plot of a representative VM neuron aligned on target onset, showing fixed visual window (red lines) and average location of fixed motor window (black lines). B) The scatter plot of differences in TG alpha values of visual (x axis) and motor (y axis) of visuomotor neurons (black circles) relative to the equality diagonal line. The average of the TG alpha values in represented by the red circle and the representative example shown in 4A-C is indicated as the red circle. Most neurons lie above the line which indicates that there is a transition from coding for target location in the visual activity to gaze end location in the motor activity within the individual VM neurons. This shift was significant (paired two tailed t test, p=0.001). This is followed by the best RF fit plots for the fixed C) visual and D) fixed motor activities.

This analysis suggests that the spatial code in SC neurons is not stable during a reactive task, particularly within VM neurons. However, it is not yet clear to what degree the overall visual motor transformation is influenced by the spatial contributions of different neuron types at different times. This is not trivial to answer, given that visual cells by definition are active before motor cells, this classification scheme and timing will interact. Does this visuomotor transformation occur because 1) neurons with early responses have a fixed T code whereas later motor neurons show a fixed G code, 2) because a distributed transformation causes a spatial shift in the code of late responses away from T, or 3) due to some combination of these factors? The first possibility (cell-fixed coding) does not seem compatible with our VM data (Figure 4D), but we performed a more in-depth analysis explore this in more detail.

TG Continuum in the full burst of visual, VM, and motor cell.

To test whether there is an overall difference in spatial coding between our three different neuron types (V, VM, M) could be influenced by a fixed neural code in each cell type, we analyzed the full burst (Figure 2) of each neuron types. In a previous paper (DeSouza, Keith et al. 2011) a similar model-fitting approach was used on the full burst of Superior Colliculus neurons during the reactive task, but that study did not use a memory-delay task to classify different neuron types, and did not provide a TG continuum analysis (only 'cardinal' models such as Te, Ge, etc.). Based on that analysis DeSouza et al. (2011) concluded that the Superior Colliculus burst primarily encodes Te, but the current analysis provides a more nuanced picture.

Figure 5 shows the 'full burst analysis' for our visual neurons (A-C), VM neurons (D-F) and motor neurons (G-I) respectively, showing an example neuron (left column), its RF at the TG value of

best fit (middle column), and the frequency distribution of TG-α for each population (right column). The entire combined population (not shown) generated a TG alpha median of 16.5 (SD=4.4), roughly in the middle of the T-G continuum (TG-alpha = 16). However, the distribution of individual neuron fits was quite broad and possibly clustered near T and G, perhaps suggesting the co-existence of different spatial codes. When these data were divided into different types, however, visual neurons (Fig. 5C) were clustered toward Te (11), with a mean TG score of 13 (SD=3.8), VM neurons (Fig. 5F) continued to show a broad distribution, with mean of 15.8 (SD= 4.9), and motor neurons (Fig. 5 I) clustered toward G (21) (mean: 17.9, SD=3.3). This analysis shows 1) that superior colliculus neurons show a broad continuum of spatial tuning between T and Ge during the reactive task, and 2) that different neuron types made a slight, significant (One-Way ANOVA, p=0.04) different contributions to this distribution, with visual cells clustering toward Te, Motor cells clustering toward Ge, and the distribution of VM cells spanning both.

Despite these tendencies, each sub-population showed a distribution of fits along the TG Continuum (Figure 5 C, G, I). To test if this was due to variations in Visual-Motor tuning within cell types, we correlated the TG fit of these cells obtained from their full burst in the reactive task against their visuomotor index (VMI) obtained from the same cells in our memory delay task (Sadeh, Sajad et al. 2015). The overall relationship is shown in Figure 5J, with each sub population coded for color. This yielded very weak correlations for visual (r^2=0.0119, p=0.7), visuomotor (r^2=0.0012, p=0.86) and motor cells (r^2=0.001, p=0.98). Even the entire cell population only showed little correlation between TG score and VMI (r^2 =0.05, p = 0.1), suggesting that the relative size of the visual vs. motor burst was not the main determining factor in the spatial codes in these cells.

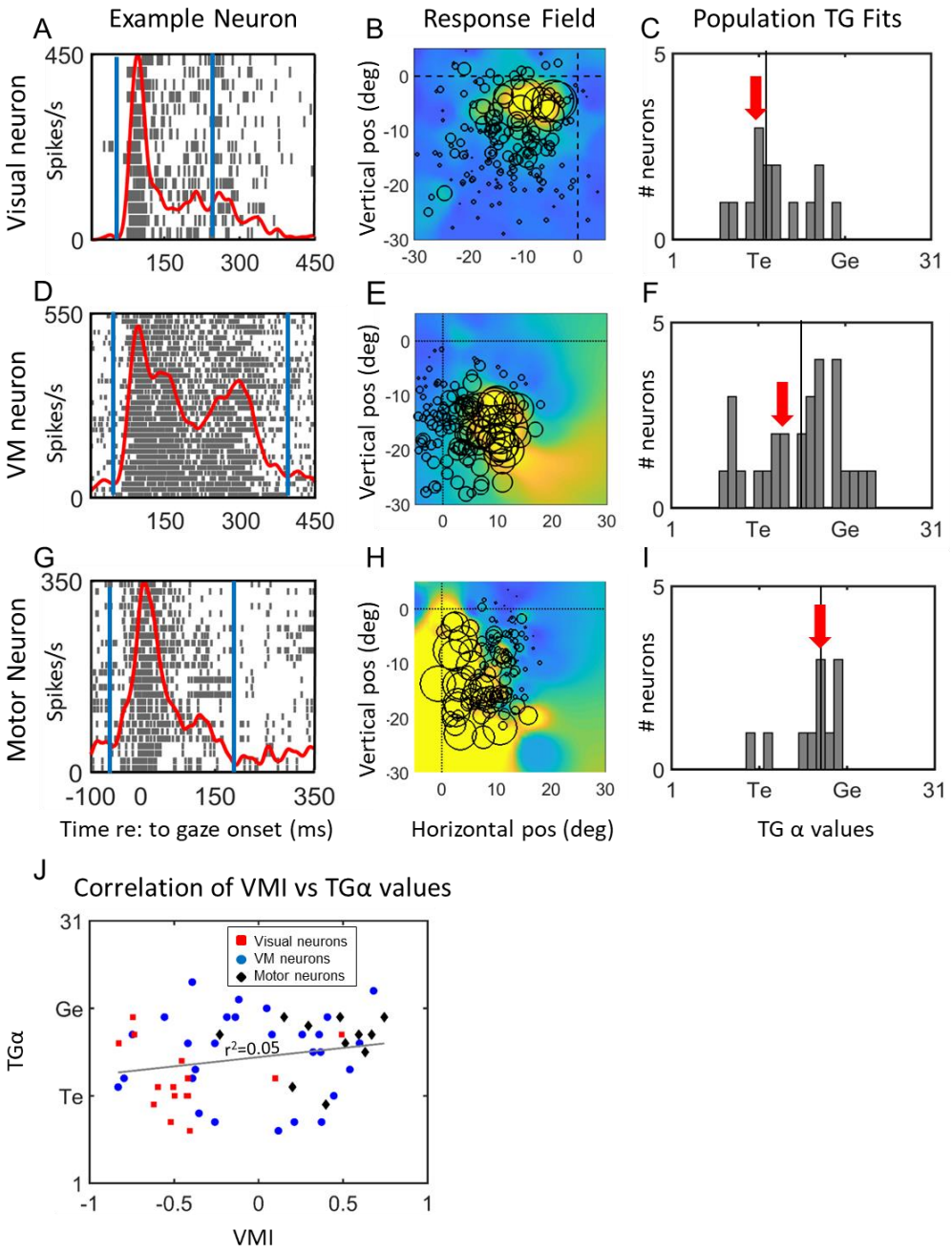

Figure 5: The TG alpha value distribution for 'full burst' analysis of neural activity in the reactive task. Spatial fits were made for each neuron, using data derived the entire duration of task-related neural activity, aligned on stimulus onset. Each plot shows a frequency histograph of best fits, along with each histogram an example of neural activity raster and the RF in the TG value indicated by red arrow on histogram are shown. A) Representative visual neuron raster, B and RF plot with C) TG alpha fits histogram for the full burst of visual neurons. D-F and G-I representative examples and histogram of TG fits for visuomotor neurons and motor neurons respectively. The vertical line in each panel indicates the median of the TG alpha values and the red arrow indicate

the TG value of the representative example. J) The correlation of TG alpha values with visuomotor index. All neuron categories exhibit a weak, non-significant correlation: Visual neurons are represented by red squares (r2=0.0119, p=0.7), VM neurons by blue circles (r^2=0.0012, p=0.86) and motor neurons by black diamonds (r^2=0.001, p=0.98). The overall correlation across all neurons (indicated by the gray correlation line) also leads a weak (r^2=0.05) non-significant(p=0.1) correlation between the two variables.

Spatiotemporal progression of visuomotor Signals in the SC.

To test if timing is the key factor in determining the spatial code in SC cells during our task, we examined the progression of spatial code through time for each neuron. Specifically, the entire activity of each of the individual neurons in each category was divided into seven time windows using a time normalization method to account for differences in duration of activity (See methods), the resultant TG alpha value was combined for each individual window in each of the neuron categories in order to investigate the temporal progression and transformation of spatial codes in each of the populations (Sajad, Sadeh et al. 2016).

Figure 6 illustrates this analysis using an example VM neuron. Figure 6A illustrates that this neuron had multiple peaks of activity, including an initial visual peak, a strong secondary visual response, and a motor response. Figure 6B shows the corresponding RFs of the first 6 windows (each plotted using is optimal fit on the TG continuum), showing how they progress through time. Figure 6 C then shows these TG fits as a function of time. Note that although these fits often 'bounce around' for individual neurons like this example, especially near the start and end where spike rate is rising and dropping and confidence is thus lowest, they show a general trend to progress from near T to nearer G, as one can see in the next analysis.

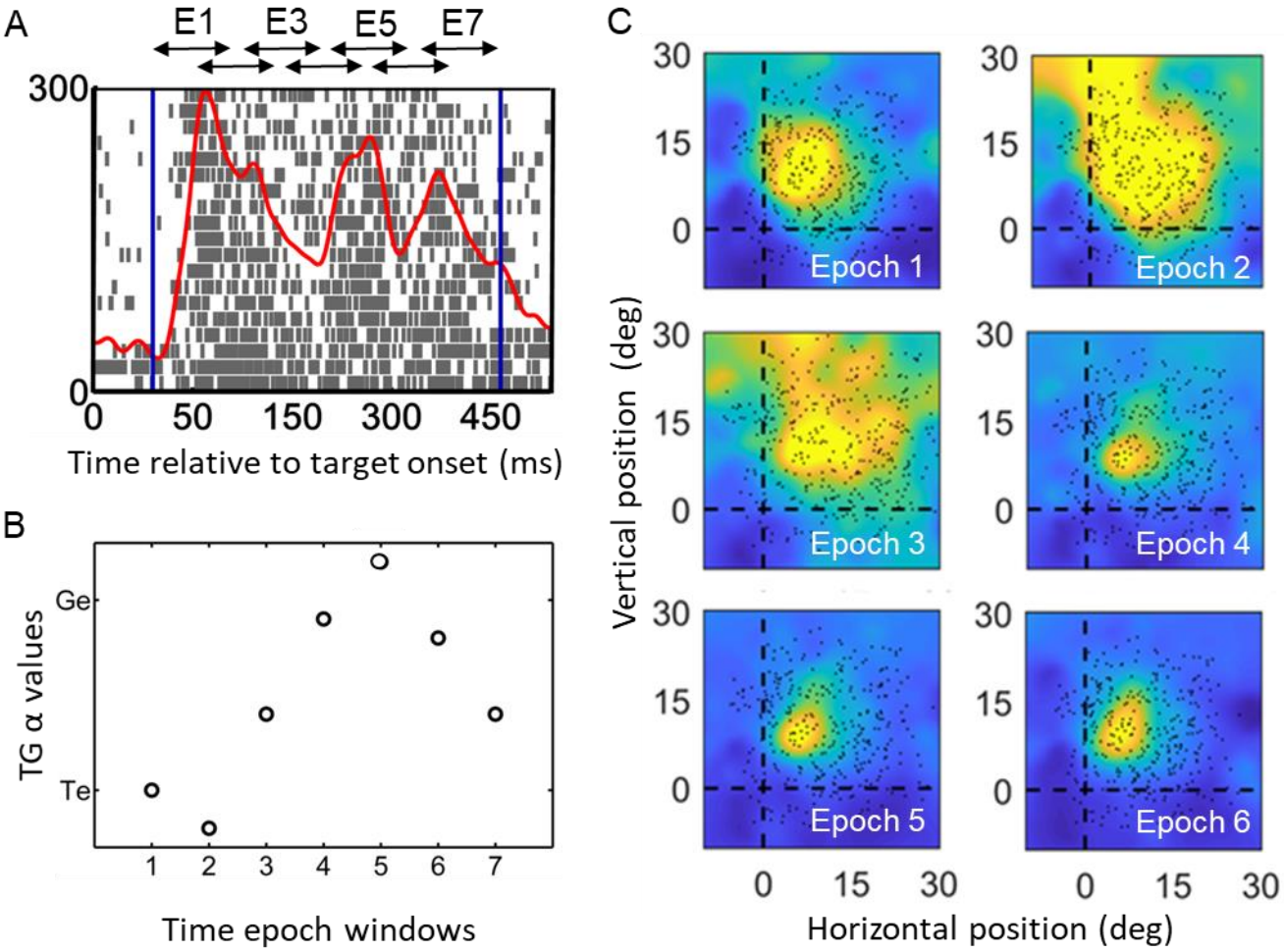

Figure 6: Spatiotemporal analysis in one example neuron. A) Action potential raster plot and spike density plot of a representative visuomotor neuron during the *reactive task*. The spike density plot (thick red line) was derived from the trials with the top 10% of activity (N=19), i.e., when the target was presented at the 'hot spot' of the RF. The dark blue vertical lines indicate the sampling window of the entire visuomotor burst. The double headed arrows on top of the raster plot indicate the semi-overlapping time windows which were used for the response filed and TG value analysis shown in B and C. These sampling windows were normalized according to the duration of the action potential (-370 to 200 ms relative to gaze onset) to yield 7 overlapping windows with equal time periods. B: TG continuum values plotted as a function of their sequence through time (1-7). In this case there is a rise from T toward G over the first 5 steps followed by a slight reversal. The details of these patterns varied across neurons. C: RF fits for the activity from time windows 1-6-, plotted in the best fit reference frame along the Target-Gaze Continuum (epoch 7 looked the same as 6). The dots indicate spatial positions of the targets in this frame for each trial and the color heat map (blue = low activity, red = high activity).

To test the temporal shift in spatial coding at the population level, we first pooled all visual, VM, and Motor cells, and looked at their progression of TG coding across the 388±53 ms duration of their response (Figure 7, first column). Most neurons showed significant spatial tuning during most time steps (bottom row), and only these were used in the TG calculation. Figure 7 A and B demonstrate the mean and median values with SD and SEM bars respectively for each of our 7 normalized time windows, and Figure C shows the percentage of data that was spatially tuned in each window (and thus included in the analysis). The trend of these results suggests a gradual progression of target related coding indicated by TG values closer to the T model (i.e. TG=11) in earlier more visually related activity to gaze coding (values closer to TG of 21) in the after activities which are temporally correlated with gaze onset. We compared the TG values in time windows 1, 3, 5 and 7 to exclude comparison between the overlapping windows using Kruskal–Wallis non-parametric one-way ANOVA test and found an overall significant difference ($p<0.0001$) between the windows. We also found significant differences in TG value of window 1 (mean: 11.1) compare to value of windows 3, 5 and 7 (means: 14.7, 19.6 and 18 respectively and $P<0.01$, $P<0.001$ and $P<0.001$ respectively). Further, the relationship between TG code and timing of the response yielded a very strong correlation ($r^2=0.94$ $p<0.00001$).

Timing vs. Cell Type

As noted above, timing and a cell classification based on visual-motor balance could interact or mask each other's effects. As a result, cell type differences could look like timing differences and vice versa. To disentangle these effects, we divided our time analysis data into separate visual (Fig 7. 2nd column), VM (third column), and motor (fourth column) populations, they each showed

similar trends, except that the 'visual' population code plateaued before reaching G. Note that over the course of our seven time steps, the percentage of spatially tuned visual cells (shown in the bottom row) peaks around the time of the late visual response and fades toward the saccade, whereas spatially tuned activity held steady in the VM population and ramped up in the motor population. Testing within the three populations, there was a significant difference between first and seventh time steps in the visual neuron population (P=0.03) and between the first and third, fifth and seventh time steps in the VM neuron population (P=0.01, P=0.001 and P=0.0001 respectively). No significant changes in the TG values were observed between the time windows in the motor neuron population, but each population showed a significant correlation as a function of timing: Visual neurons: r^2=0.6, p=0.0006, VM neurons: r^2=0.81, p<0.00001, and Motor neurons: r=^{2}0.96, p<0.00001.

Based on visual inspection, there appears to be a slight upward shift (from T toward G) in these time-normalized plots from visual (Fig. 7 B), to visuomotor (Fig. 7C), to motor (Fig. 7 D) populations. However, there was no significant difference between these plots (P = 0.53, Non-parametric One-way ANOVA test test). These results suggest that a similar spatiotemporal progression occurs across different cell types in the SC during reactive saccades, and that the difference in spatial coding across different cell types (Figure 3) are primarily due to the relative timing of their responses, rather than fundamental differences in neuron properties.

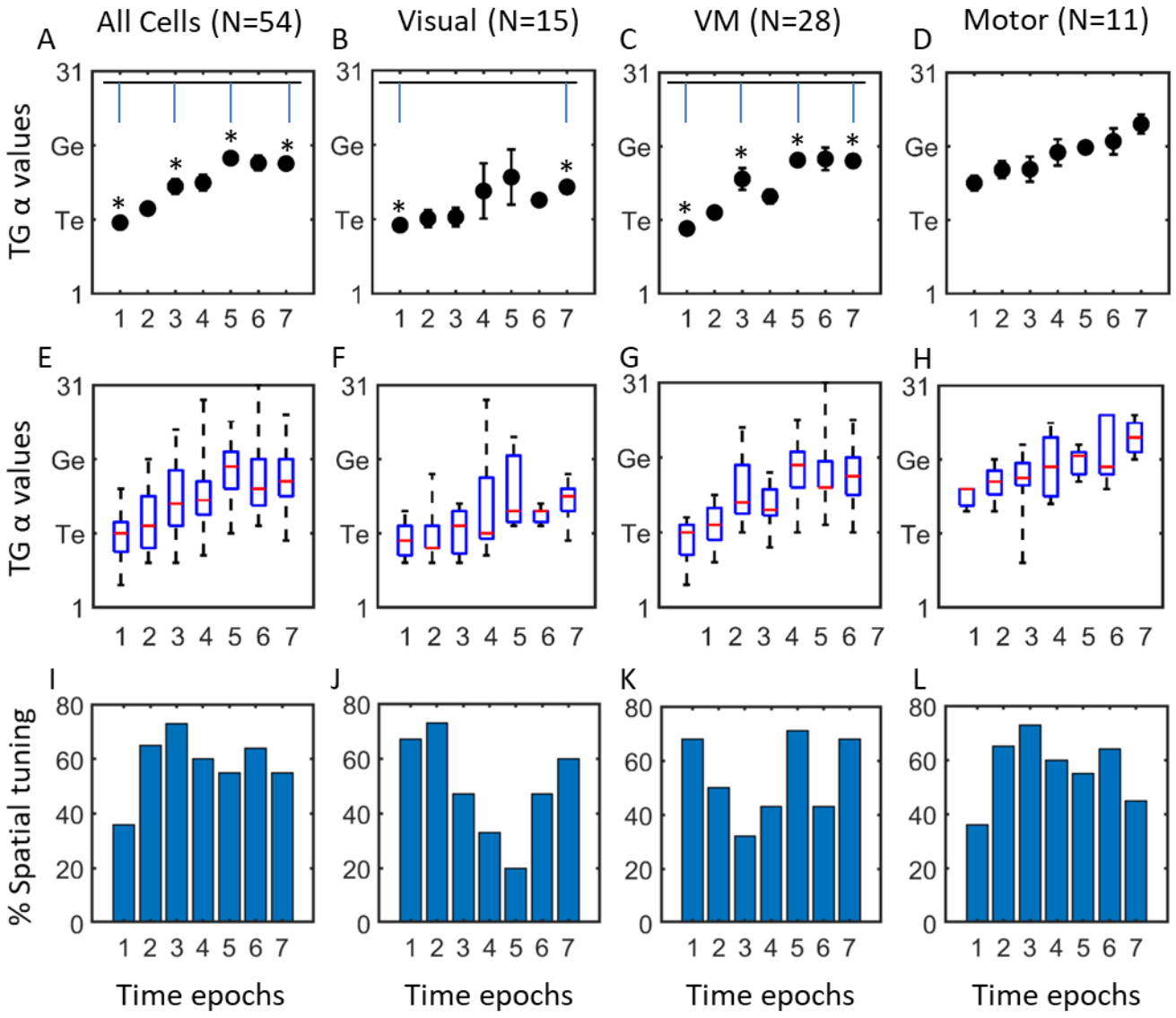

Figure 7: Spatiotemporal analysis in entire superior colliculus neuron population (*column 1*) and each sub-population (*columns 2-4*). *Top row* (A-D) shows the mean TG alpha values (y axis) of each temporal window of analysis (x axis) with SEM bars, the *middle row* (E–H) shows the median values (red bars) as well as first and third quartiles (blue bars) of TG alpha values (y axes) for the same data, and the *bottom row* (I-L) shows the percentage of cells in each time epoch that showed significant spatial tuning. The entire neuron population (*Column 1,* N=56), showed a gradual shift in each step from more Te related coding in the earlier visual activity to more Ge related as the activity becomes closer to gaze onset. The Visual neuron population (*Row 2*, N=15) which showed a predominantly preference in coding for target especially in earlier windows with a non-significant shift toward intermediate TG alpha value later in its activity (one-way ANOVA p=0.402). The VM population (*Row 3*, N=28) showed a significant shift in TG alpha values (One-way ANOVA p=0.0001). The Motor population (*Row 4*, N=11) started at a more intermediate TG

value and showed a non-significant shift toward G (one-way ANOVA p=0.48). The significant differences in TG values between time epochs (P<0.05) are indicated by asterisk (*). However, as described in the text, there was no significant difference between these three patterns. Note that for the results shown in Fig 5A-H, the TG values were included in the analysis only if the neuronal activity showed spatial tuning for that given analysis window.

3-7 Discussion

The process of transforming the visual information into movements command must occur for a successful and timely gaze shift (Mays and Sparks 1980, Gnadt, Bracewell et al. 1991, Crawford and Guitton 1997, Pouget and Snyder 2000, Snyder 2000, Crawford, Henriques et al. 2011, Sajad, Sadeh et al. 2015, Sajad, Sadeh et al. 2016). Here we found that the superior colliculus (SC) participates in a rapid transformation from target to gaze coding, even in the absence of a memory delay or other experimental manipulations. Further, we have shown this does not primarily arise because of some fixed intrinsic code within in different cell types (at least along the visual-visuomotor-motor continuum) but rather because of a continuous temporal progression through all cell types. To our knowledge, this is the first direct demonstration of an internal spatiotemporal transformation during simple reactive saccades.

The Superior Colliculus Spatial Code

It has been a subject of debate whether the SC codes T, target location (Sparks and Porter 1983, Waitzman, Ma et al. 1988, Sparks 1989, Basso and Wurtz 1998, McPeek and Keller 2004) or G, future gaze location (Walker, Fitzgibbon et al. 1995, Freedman and Sparks 1997, Everling, Dorris et al. 1999, Horwitz and Newsome 1999, Klier, Wang et al. 2001). In a previous study (DeSouza et al. 2011), we concluded that overall SC activity preferred a Te code during reactive saccades.

In light of the current study, this was likely due to a mixture of different signals and the use of cardinal T and G models rather than the T-G continuum. The current more sophisticated analysis revealed a continuum of T-G codes across all three cell populations, with a preference for T in V cells, a distribution that equally spanned T and G in VM cells, and a preference for G in M cells. This is generally consistent with our analysis of SC activity in a memory delay task (Sadeh et al. 2016), and makes sense in terms V cells presumably reflecting visual input most closely (Wurtz and Mohler 1976, Wurtz and Albano 1980, Moschovakis, Karabelas et al. 1988), motor cells reflecting output (Sparks and Hartwich-Young 1989, Miyashita and Hikosaka 1996, Sparks 2002), and VM cells reflecting both as well as more complex influences. VM neurons are known to receive a more extensive range of inputs from other brain areas (Wurtz and Albano 1980, Moschovakis, Karabelas et al. 1988, Moschovakis, Karabelas et al. 1988, Sparks 2002), have diverse subtypes(Sparks 1978, Wurtz and Albano 1980, Sparks and Hartwich-Young 1989, Munoz and Wurtz 1995, Munoz and Wurtz 1995) and are suggested to be more involved in cognitive and higher order functions (Everling, Dorris et al. 1999, Horwitz and Newsome 1999, Krauzlis, Liston et al. 2004, Sommer and Wurtz 2004, Krauzlis, Lovejoy et al. 2013, Dash, Yan et al. 2015).

Evidence for a visual to motor transformation in the superior colliculus

One traditional view of spatial coding in the SC is it codes retinal error information received from retina and striate cortex, and simply relays this to the brainstem (Mohler and Wurtz 1977, Distel and Fries 1982, Fries 1984, Waitzman, Ma et al. 1988, Optican 1995; Sparks 2002; DeSouza et al. 2011). Alternatively, it has been demonstrated that the SC (and other cortical gaze areas) can provide a visual-motor transformation for gaze shifts when the experimental task introduced a

temporal or spatial separation between the visual stimuli and movement initiation (Gnadt and Andersen 1988, Everling, Dorris et al. 1999, Everling and Munoz 2000, Munoz and Everling 2004, Sadeh, Sajad et al. 2015, Sajad, Sadeh et al. 2016, Sajad A 2016). However, it has been argued that the separation of visual and motor events required in these studies influences spatial code by changing the cognitive demands on the neural circuit, for example forced encoding the target of location by visual activity and the gaze movement by motor activity in the case of anti-saccades, or by introducing memory-related errors in the case of a the memory-delay task (Mays and Sparks 1980, Stanford and Sparks 1994, White, Sparks et al. 1994, Goldman-Rakic 1995, Miller, Erickson et al. 1996, Brown, DeSouza et al. 2004, Hollingworth 2015, Sajad, Sadeh et al. 2016, Sajad A 2016).

The current study utilized a simple behavioral paradigm (reactive gaze saccade made directly to targets with no delay), combined with a sensitive model-fitting approach that can track spatial codes based only on endogenous error in the system. Based on the results of our previous study, which tested a wide array of spatial models in a memory delay task (Sadeh et al. 2015) we focused on two models: Target in eye coordinates (Te) and future gaze position in eye coordinates (Ge), and used 'TG' continuum between these models to test the visuomotor transformation. The results were clear, even in the short time span (192 ± 23 ms) between our visual and motor analysis windows there was a significant shift in coding across our entire population from T toward a G code. Given the simplicity of the task these cannot be attributed to exogenous suppression, memory, or top-down transformation signals. Instead, we attribute these errors to a transformation occurring within the sensorimotor circuit. Since the output (Ge) still encodes gaze in retinal coordinates, this remains compatible with the notion that the SC provides a two

dimensional command to the brainstem in retinal coordinates (Klier, Wang et al. 2001), which is then elaborated into separate but coordinated three-dimensional commands for eye and head rotation by the brainstem and cerebellum(Optican and Quaia 2002, Klier, Wang et al. 2003). Given that our analysis separates T and G based on endogenous variable gaze errors, this suggests that the SC (or a circuit that includes the SC) is involved in producing those errors. Conversely, we cannot conclude that our transformation result generalizes to all situations with different tasks and error types.

What produces the TG transformation?

In this study we can only comment directly on SC data, but the sensorimotor transformations for gaze likely involve its reciprocal connections to the frontal eye fields, cerebellum, and thalamus, as well as feedback from the brainstem (Munoz and Guitton 1985, Schall and Thompson 1999, Optican and Quaia 2002, Schall 2002, Sommer and Wurtz 2002). It has been suggested that studies which separated sensory and motor produced a transformation by activating separate circuits of cells to code different spatial variables (Pierrot-Deseilligny, Rivaud et al. 1991, Gaymard, Ploner et al. 1999, Ohbayashi, Ohki et al. 2003, Bays, Gorgoraptis et al. 2011, Barber, Caffo et al. 2013, Sajad, Sadeh et al. 2016, Sajad A 2016). To test if this was also the case here, we compared overall spatial coding in visual (V), visumotor (VM), and motor (M) neurons, but concluded this had little direct influence on the spatial code in this particular task. This need not always the case: in the FEF we found that visuomotor and motor cells code different spatial attributes at the end of a memory delay (Sajad et al. 2016). At this time, it cannot be said whether this difference is due to the difference in brain structures, or different tasks. Further, based on

our data we cannot exclude the possibility that some other cell classification scheme might explain spatial coding better, or that V, VM, and M cells might make different contributions to some other gaze task.

When viewed as a spatiotemporal transformation (Figures 7 and 8), it became clear that the main determining factor for the SC spatial code during the reactive task was timing. This was distributed throughout different cell types and was perhaps most surprising in cells that fell within our visual classification. The most likely explanation for this is that the SC is involved in a noisy, distributed sensorimotor transformation(Burns and Blohm 2010, Franklin and Wolpert 2011) that includes lateral and recurrent connections(Harting 1977, Harting, Huerta et al. 1980, Meredith and Stein 1983, Fries 1984, May 2006). In this scenario, a major component of variable gaze errors results from the rapid accumulation and general spread of noise during the transformation from visual inputs to motor outputs, and we see this reflected in all of our SC cells. This noise is relative small during normal gaze shifts, but could become quite large during certain clinical conditions (Ketcham, Hodgson et al. 2003, Rottschy, Kleiman et al. 2013, Avery and Krichmar 2015) For this reason, the analysis tools used here could be useful for detecting biomarkers of the source of sensorimotor function in the affected circuits.

Conclusions

To our knowledge, this is the first study to track the spatiotemporal code in superior colliculus cells during simple reactive saccades toward a briefly flashed target, demonstrate a rapid visuomotor transformation, and trace this to the accumulation of errors in a distributed SC circuit rather than a relay between cells with fixed spatial codes. We cannot say if these results

generalize to other brain areas, tasks, and motor behaviors, but given the relative simplicity of our task and the evolutionary conservation of SC function, it seems likely that similar processes occur alone or in conjunction with other transformations in many other areas and behaviors.

Chapter 4

The influence of a memory delay on spatial coding in the superior colliculus: is visual always visual and motor always motor?

Morteza Sadeh, Amirsaman Sajad, Hongying Wang, Xiaogang Yan and John Douglas Crawford

(Manuscript Submitted to Frontiers in Neural Circuits)

4.1 Abstract:

The memory-delay saccade task is often used to separate visual and motor responses in oculomotor structures such as the superior colliculus(SC), with the assumption that these same responses would sum with a short delay during immediate 'reactive' saccades to visual stimuli. However, it is also possible that additional signals (suppression, delay) alter visual and/or motor response in the memory delay task. Here, we compared the spatiotemporal properties of visual and motor responses of the *same* SC neurons recorded during both the reactive and memory-delay tasks in two head-unrestrained monkeys. Comparing tasks, visual (aligned with target onset) and motor (aligned on saccade onset) responses were highly correlated across neurons, but the peak response of visual neurons, and peak motor responses (of both visuomotor and motor neurons) were significantly higher in the reactive task. Receptive field organization was generally similar in both tasks. Spatial coding (along a Target-Gaze continuum) was also similar, with the exception that pure motor cells showed a stronger tendency to code future gaze location in the memory delay task, suggesting a more complete transformation. These results suggest that the introduction of a trained memory delay alters both the vigor and spatial coding of SC visual and motor responses, likely due to a combination of saccade suppression signals and greater signal noise accumulation during the delay in the memory delay task.

4.2 Introduction

The primate superior colliculus (SC) has been studied extensively both for its specific role in generating saccades and head-unrestrained gaze shifts, and as a general model for sensory-motor transformations (Mays and Sparks 1980, Wurtz and Albano 1980, Optican 1995, Marino, Rodgers et al. 2008, Sadeh, Sajad et al. 2015). One defining characteristic of the SC is that its neurons can be categorized into populations with only 'visual' responses (briefly delayed burst responses to a visual stimulus), only 'motor' responses (burst activity just before and after a saccade) or visuomotor responses, i.e., both visual and motor (Wurtz and Goldberg 1972, Wurtz and Goldberg 1972, Sparks 1978, Harris 1980, Wurtz and Albano 1980, Bruce and Goldberg 1985, Bruce, Goldberg et al. 1985, Munoz and Wurtz 1995, Munoz and Wurtz 1995, Stricanne, Andersen et al. 1996, Freedman and Sparks 1997, Gandhi and Katnani 2011, Bremmer, Kaminiarz et al. 2016). Implicit in this categorization is the assumption that these responses are task-independent, but this is not necessarily the case. Here, we specifically examined whether the task typically used to separate these cell types might itself influence their neural code, and conversely, whether these responses code something different in simpler gaze saccades.

The typical way to separate visual and motor responses is to introduce a memory delay between a transient visual stimulus and the gaze saccade (Wurtz and Goldberg 1972, Sparks 1978, Wurtz and Albano 1980, Sparks and Hartwich-Young 1989, Stanford and Sparks 1994, Munoz and Wurtz 1995, Munoz and Wurtz 1995, Sajad, Sadeh et al. 2015). Delays of 500-1500 ms provide a clean temporal segregation between the visual response and/or motor response. The addition of a spatially separation between the visual stimulus and the saccade vector across the memory delay (e.g. using a double step saccade task or the anti-saccades task) likewise separate the spatial

tuning of visual and motor responses (Everling and Munoz 2000, Munoz and Everling 2004) More recently, we have shown that even in the absence of these spatial manipulations, the SC visual response encodes target location relative to initial eye orientation whereas after a memory delay the motor response encodes future gaze direction relative to current eye orientation (Sadeh, Sajad et al. 2015).

Saccades made immediately and directly to a transient visual stimulus, without a memory delay, are called 'reactive saccades'(Sparks 1978, Pierrot-Deseilligny, Rivaud et al. 1991, Deubel 1995, Munoz and Wurtz 1995, Munoz and Wurtz 1995, Sadeh, Sajad et al. 2018). During such saccades there is typically a 25-50 ms peak-to-peak delay between visual and motor responses, although this is prolonged during head unrestrained gaze shifts (Freedman 2008, DeSouza, Keith et al. 2011, Sadeh, Sajad et al. 2018). In either case, there is significant temporal overlap between these responses. As a result, visuomotor cells often show a continuous burst, but often with a slight inflection between peaks that correspond in time to the visual and motor burst (Sparks 1978, Munoz and Wurtz 1995, Munoz and Wurtz 1995, Dorris, Pare et al. 1997, DeSouza, Keith et al. 2011). Often, investigators use such inflections to arbitrarily draw a 'line' between visual and motor responses, knowing very well that they might actually blend into each other (Mays and Sparks 1980, Everling, Dorris et al. 1999, Marino, Rodgers et al. 2008, DeSouza, Keith et al. 2011, Marino, Levy et al. 2015, Sadeh, Sajad et al. 2015). It is generally assumed that these responses summate linearly in reactive saccades. This assumption seems to be supported by our recent finding that during reactive saccades, SC cells show a transition from target coding in their visual response to gaze coding in their motor responses (Sadeh, Sajad et al. 2018) similar to that observed previously after a memory delay(Sadeh, Sajad et al. 2015). However, in the absence of

a direct comparison, it cannot be assumed that the spatial codes of SC visual and motor responses are quantitatively identical both with and without a memory delay.

First, the temporal overlap between visual and motor signals in visuomotor cells might influence their respective codes. For example, visuomotor cells showed a progressive transition between intermediate target-gaze codes during both reactive and memory delay saccades, but with very different time courses (Sadeh, Sajad et al. 2015, Sadeh, Sajad et al. 2018). This could lead to greater overlap in visuomotor cell codes in the reactive task. Conversely, the addition of a memory delay likely introduces additional signals that could influence spatial codes. These include saccade suppression signals that could influence the vigor of both visual and motor responses (Thiele, Henning et al. 2002, Munoz and Everling 2004), and memory delay / motor build up activity that might specifically influence the final motor response(Munoz and Wurtz 1995, Munoz and Wurtz 1995, Miller, Erickson et al. 1996, Pesaran, Pezaris et al. 2002, Sajad, Sadeh et al. 2016, Sajad A 2016). In the past it was not possible to test all of these predictions, because the technology was lacking to probe specific visuomotor codes in the absence of additional spatial manipulations.

In the current study we investigated if the visual and motor responses observed in reactive saccades altered, either in amplitude or spatial content, by the insertion of a memory delay. To do this, we recorded from the same SC neurons using both the reactive and memory delay tasks, and analyzed and directly compared their firing rates and spatial content. We did this using an analytic approach based on variable gaze errors that allowed us to fit activity from specific visual and motor response epochs against models along a visual-motor continuum (Keith and Crawford

2008, DeSouza, Keith et al. 2011, Sadeh, Sajad et al. 2015, Sajad, Sadeh et al. 2015). This was done in head unrestrained animals because this reflects a more natural behavioral condition, allowed us to eliminate some other models in our initial analysis (Sadeh et al. 2016), and in this specific case provided more prolonged and temporally rich response profiles for our analysis. We found that, although certain fundamental aspects are retained in visual and motor responses (such as the preference for target vs. gaze coding) the addition of a memory delay does introduce subtle alterations to the amplitudes and spatial codes of SC signals, particularly in the motor responses, which may influence behaviour.

4.3 Methods

Animals and Surgical Procedures

The data were collected from two female monkeys (Macaca Mulatta, M1 and M2; age, 10 years; weights, 6.5 and 7 kg) with a protocol approved by the York University Animal Care Committee in accordance with guidelines published by the Canadian Council for Animal Care. With similar surgical procedures as described previously (Crawford, Ceylan et al. 1999, Klier, Wang et al. 2001), the monkeys were prepared for long-term electrophysiology and 3D gaze movement recordings. Each monkey was subjected to general anesthesia with 1–2% isoflurane after intramuscular injection of ketamine hydrochloride (10 mg/kg), atropine sulphate (0.05 mg/kg), and acepromazine (0.5 mg/kg). To minimize the collisions between experimental setup and Microdrive/electrode we implanted a vertically aligned unit recording chamber (i.e. with no tilt) placed 5 mm anterior and 0 mm lateral in stereotaxic coordinates, which allowed access to the left and right SC. This chamber angle and position were chosen to minimize collisions between

the electrode/microdrive and the experimental setup during head movements, and to simplify the use of stereotaxic coordinates during recordings. The chamber was then surrounded by a dental acrylic cap, which was anchored to the skull with 13 stainless steel cortex screws. Two scleral search coils (diameter, 5 mm) were implanted in one eye of the monkeys to record 3D eye movements. Two orthogonal coils, which were secured with a screw on a plastic base on the cap, recorded the 3D head movements during the experiments. 3D recordings and analysis were performed as described previously (Crawford, Ceylan et al. 1999, DeSouza, Keith et al. 2011).

Experimental equipment

We used a Pentium IV PC and custom-designed software to present stimuli, control behaviour paradigms, send digital codes to a Plexon data acquisition system, and deliver juice rewards to the monkeys. Stimuli were presented on a screen 60 cm in front of the monkey, by use of a projector (WT600 DLP projector; NEC). Monkeys were seated on a custom-designed primate chair in order to have their heads move freely at the centre of a 1-m^3 magnetic field generator (Crawford et al., 1999), and a juice spout (Crist Instruments) was placed on the skull cap for computer-controlled delivery of the juice reward to the monkey's mouth.

Behavioural recordings ad paradigms

All experiments were performed using 3D recordings in head-unrestrained conditions (Crawford et al. 1999; Sadeh et al. 2016). Head motion was not analyzed in the current experiment, but provided some advantages: for comfort, natural system behavior, adequate range of gaze motion for testing large neural response fields (RF; see below). Conversely, 3D recordings and analysis were required, to account for the significant torsional eye rotation and prominent non-linearities

that occur in the head unrestrained gaze range (Tweed and Vilis 1987; Crawford et al. 1999; Klier et al. 2001; Keith et al. 2009; DeSouza et al. 2011). The target-relative-to-eye (Te) and gaze-relative-to eye (Ge) models tested in this study were computed by rotating (not subtracting) a vector pointing from the eye toward the target or future gaze position by the inverse of initial 3D eye orientation (Klier, Wang et al. 2002).

All neurons described in the current study were tested in both of the following two paradigms:

Reactive task (Figure 1 A, C). Animals were trained to fixate a central range of positions for 900-1000 ms (randomly varied interval). A tolerance window of 2–4° (radius) with respect to the fixation position was required during this period. Simultaneous with initial fixation point disappearance-serving as GO signal-a target (red circle with a size of 0.5°) was presented in the periphery for 125 ms, at locations selected for RF mapping (Figure 1 C; see below for details). Animals were then required to make a gaze shift toward the briefly flashing stimulus and fixate on it for 200 ms in order to receive juice reward. In order to spatially separate targets vs. gaze coding, we designated a relatively wide tolerance window of 6–12° (diameter) for gaze errors around the locations of the targets, and thus allowed monkeys to produce a self-selected distribution of gaze end point errors around the targets (See Figure 1A, C, D).

Memory delay task (Figure 1 B): The conditions, fixation point and stimulus characteristics in this task were identical to the reactive task except that after 300 ms of fixation, a target stimulus appeared in the periphery for 125 ms. The fixation light remained on for another 400–700 ms in order to introduce a variable memory delay and discourage anticipation of the go signal. When the GO signal was presented, the monkeys made a gaze shift towards the remembered location

of the target, and were required to maintain fixation for at least 200 ms at that final position to obtain the juice reward.

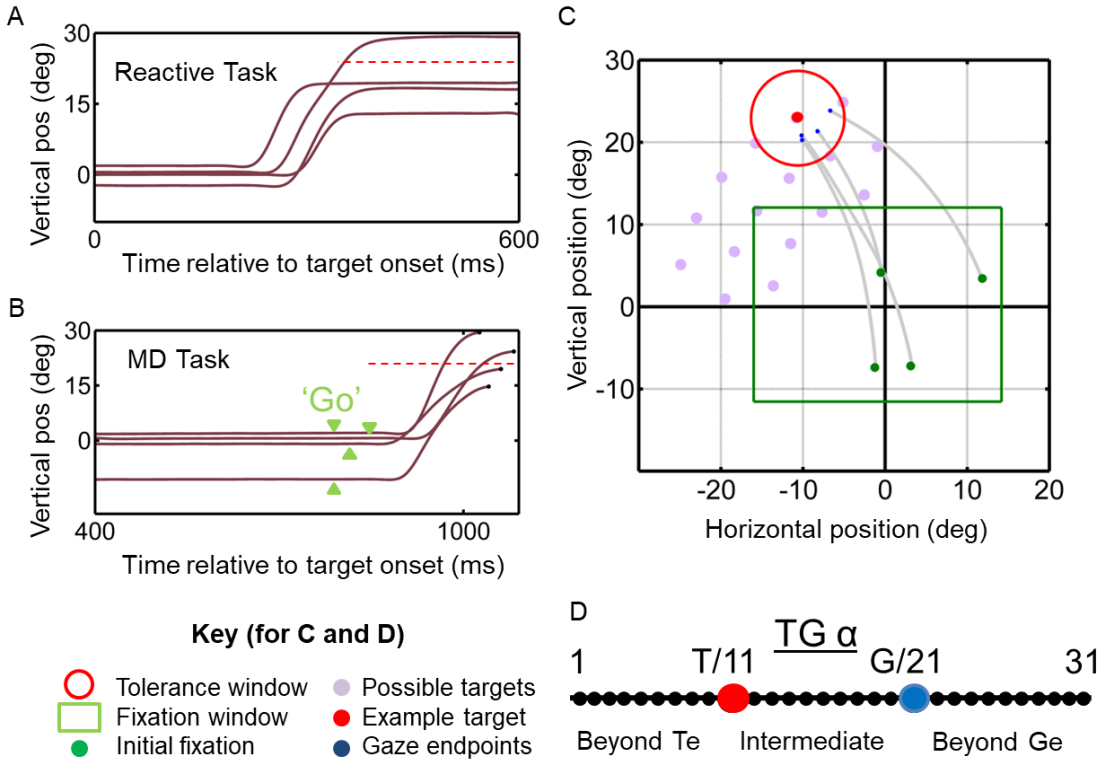

Figure 1: Temporal (A/B) and spatial (C/D) aspects of the behavioral tasks. A) Vertical gaze position toward an upward target (dashed red horizontal line) plotted as a function of time for example trials in the *reactive task*. Results from this task are reported in Sadeh et al. (2018). B) Similar gaze traces for the same target, but obtained from the *memory delay task*. Note that the memory delay is variable, so the 'go' signal (extinction of the fixation point) occurred at different time points (green arrow heads). Results from this task were reported in detail previously (Sadeh et. al. 2016). C) Two-dimensional gaze trajectories (grey lines) from the *reactive task* for an example target in monkey M2. Also shown are the range of initial fixation positions (green square), the tolerance window (red circle), and the other possible targets used in this experimental session (grey circles) to map a neuron's receptive field. The identical spatial layouts were used for both tasks to test each neuron. D) Target-Gaze continuum constructed between and beyond target position (red dot) and gaze end point (blue dot) for each trial, and used to determine best fits for neural receptive fields.

Data from these two tasks were described previously (Sadeh et al. 2016; Sadeh et al. submitted), but this is the first time that we provide a direct quantitative comparison.

Off-line trial definition and inclusion criteria

During our off-line analysis the beginning of a trial was defined by the appearance of the initial fixation point. The beginning of the gaze saccade was defined as the instant when its velocity exceeded 50°/s, and its end when its velocity decreased to 30°/s. All trials were considered for analysis irrespective of whether the monkey received a reward after the trial. We excluded trials based on spatial and temporal criteria. First, trials in which the directions of the gaze shifts were completely unrelated to the direction of the target (e.g. opposite direction) were removed. Then, we obtained the regression between errors in gaze vs. retinal error (the retinal angle between the fovea and the target at the initial position before the gaze shift), and removed trials with gaze error two standard deviations greater than this regression line. Furthermore, every trial was visually inspected, and any trial in which the gaze shift was anticipated (reaction time of < 100 ms after the go signal) and when the gaze shift consisted of multistep saccades was excluded from the analyses described below.

Neural recordings and receptive field mapping

We recorded extracellular activity from the left and right SC with tungsten microelectrodes (FHC). The electrode was inserted through a guide tube, which was controlled by a hydraulic microdrive (MO- 90S; Narishige International, East Meadow, NY, USA). Isolated signals were amplified, filtered and stored for off-line sorting with the Plexon MAP system. The SC was identified according to criteria published previously (DeSouza, Keith et al. 2011, Sadeh, Sajad et al. 2015).

The steps of SC identification and confirmation are identical to those explained previously (Sadeh, Sajad et al. 2015). Once an SC neuron was isolated, the target stimuli were presented in the visual field contralateral to the hemi field of the recording site to begin RF mapping. RFs were estimated through initial mapping, which involved monkeys performing visually guided saccades to a wide range of stimuli presented on the screen while cell activity was monitored on-line. Test stimuli were then selected within a grid (12–32 targets, depending on the RF size) that extended just beyond the cell's receptive field. Figure 1 C illustrates the array of target used for one particular cell in the reactive task. During testing, stimuli were presented in a randomized order, and each target was presented for at least seven gaze shifts. The *MD* task was done first in all experiment sessions in order to separate the visual and motor bursts and characterize the neuron type, the behavioral task that ran after wards were randomized for each given experiment session.

Neuron Classification

The memory delay saccade task was used to dissociate between visual and movement related activities and categorize cells into visual, visuomotor (VM) and motor neurons. Visual neurons were defined as cells that showed a robust burst of activity (> 50 spikes/s above the baseline) 40– 60 ms after the stimulus presentation that lasted for ~180 ms afterwards(Goldberg and Wurtz 1972). Motor neurons were those with robust activity or a buildup of activity peaking around the time of gaze onset, with activity starting prior to the gaze onset (100–40 ms before saccade), and that continued to ~100 ms after gaze onset. Neurons that met both of these criteria were classified as visuomotor. When we refer to 'number of spikes' below, this refers to number

of action potentials in these defined temporal windows, also we use neural activity and burst interchangeably to refer to the same concept of action potentials.

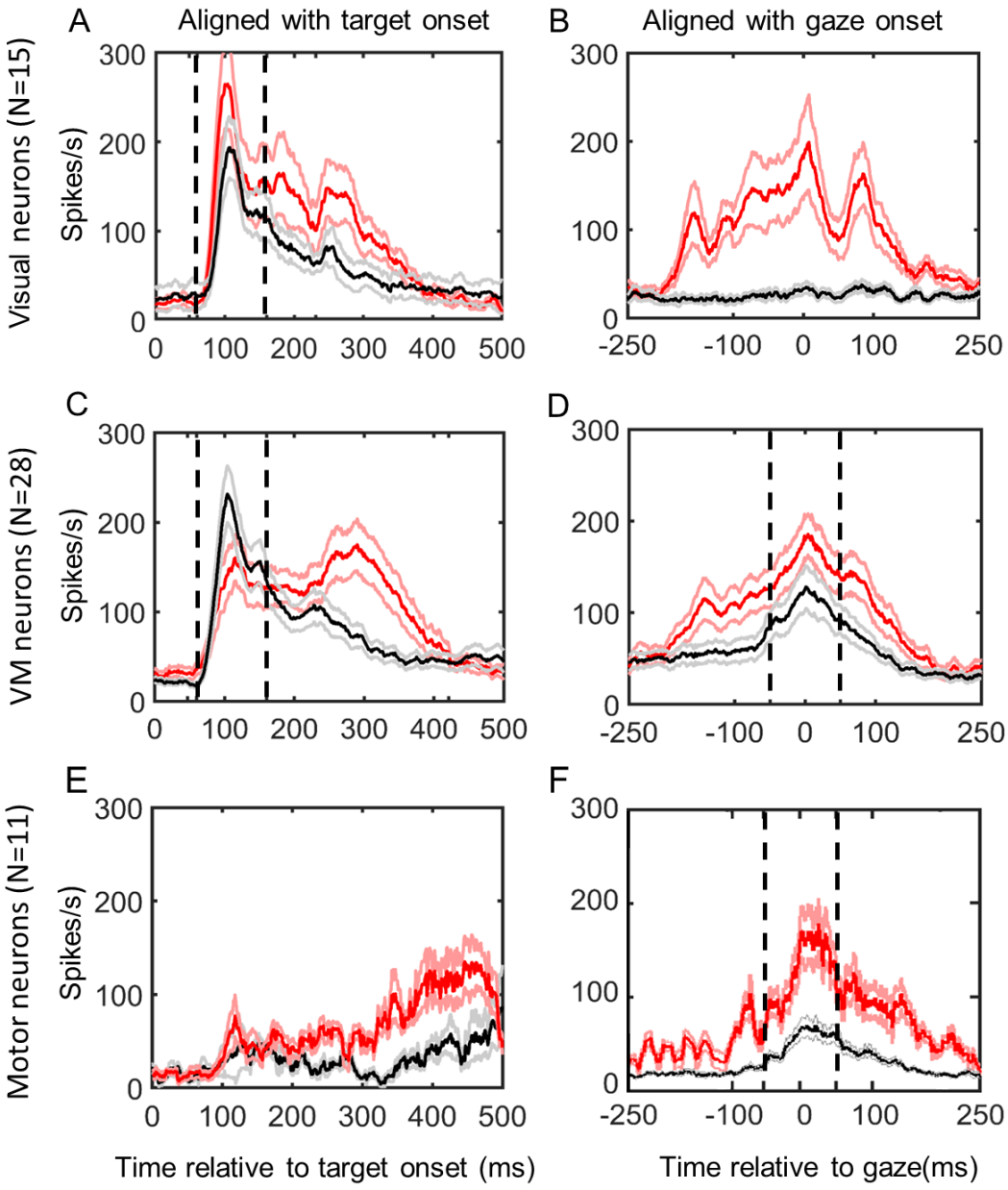

Figure 2: Mean spike density plots / 10% confidence intervals from the same neurons in the *reactive task* (red/pink) versus the memory delay task (black/gray). Data aligned with stimulus onset (left column) and gaze movement (right column). *Top row* (A/B): Visual neurons, N=15; *Middle row* (C/D): Visuomotor neurons (N=28); Bottom Row (E/F): Motor neurons (N=11), identified using the memory delay task (Sadeh et al. 2016). Dashed vertical lines indicate the time intervals used for the 'fixed window' visual (60 to 160 ms relative to target presentation) and motor (-50 to +50 ms relative to gaze onset) analyses.

Temporal Windows for Neural Analysis

The temporal windows that we used for analysis of bursting activity are illustrated in the results section (Figure 2). We used a fixed window of +70 to +170ms relative to visual target presentation for visual activity and +/-50 ms relative to saccade onset (indicated as black vertical dashed lines on Figure 3, 5, and 6). In some cases, the entire duration of the reactive saccade burst was marked by an observer for comparison with the memory-delay data.

Spatial Analysis of Neuronal Response Fields: the TG Continuum

Visual and motor RFs were obtained for each neuron (using the temporal windows described above) and analyzed using a method that has previously been described several times (Keith, DeSouza et al. 2009, DeSouza, Keith et al. 2011, Sadeh, Sajad et al. 2015, Sajad, Sadeh et al. 2015). Briefly, the RF of the neuron was plotted by overlapping firing rate data over two-dimensional position data corresponding to the spatial parameter related to the given model, such as final gaze position relative to the eye. The quality of the model for the data was quantified by calculating the Predicted Sum of Squares (PRESS) residuals for all trials, which is a type of cross validation in regression analysis (Keith, DeSouza et al. 2009) . Specifically, the PRESS residual for a single trial was obtained by: 1) eliminating that trial from RF data, 2) fitting the remaining data points non-parametrically using Gaussian kernels at various bandwidths (2-15°), and 3) obtaining the residual between the fit and the missing data point. The overall predictability power of the model for the recorded data set was quantified by the average of PRESS residuals across all trials for that neuron. Once PRESS residuals of all the spatial models were obtained the spatial code of a neuron was then defined as the model (at the kernel bandwidth) that yielded the overall best

fit (i.e. smallest residual) to the data. In order to characterize the spatial coding of the population of neurons the final step of our analysis involves combining the results of individual neurons in order to obtain the best fit model of that population (Keith, DeSouza et al. 2009)

Our previous studies have tested various spatial models of SC activity but have found the spatial continuum spanning the location of the target and the eventual gaze endpoint (i.e., *target-gaze (TG) continuum*) defined in eye-centered coordinates to be most useful in distinguishing visual from motor coding (Sadeh et al. submitted). The physical basis of the TG continuum is illustrated in Figure 1 C, which shows the TG continuum for an example trial in space coordinates, which would look similar when rotated into eye coordinates (Klier, Wang et al. 2001). This continuum extends between, and beyond T and G position for every such trial, based on our behavioral measures. As described previously (Sadeh, Sajad et al. 2015, Sajad, Sadeh et al. 2015), in our analysis the TG continuum was constructed by extending the possibility of the best fit for neural activity between and beyond target and gaze models within the same reference frames (eye coordinates). The intermediate spatial models were constructed by dividing the distance between target position and final gaze position for each trial into 10 equal intervals and 10 additional intervals extended on either end. Depending on the location of a neuron on the continuum a value (here referred to as TG alpha value), between 1 to 31 (the Target and Gaze locations are arbitrarily numbered 11 and 21 respectively) which indicates their relative preference for coding target vs. gaze related spatial information. For example, if the fit and TG continuum analysis for the activity of a given neuron yields the value of 20, this indicates that the spatial information encoded by this neuron's activity is regarding the target location information rather than gaze endpoint information. Once the optimal TG value is determined, it can then be

used to plot each neural RF in its intrinsic coordinate system, by plotting activity for each trial according to its location along the TG continuum (in eye-centered coordinates).

This TG continuum analysis is insensitive to systematic gaze errors and will automatically adjust to any magnitude of variable error, so long as the range of these errors sufficiently exceeds the noise range of the gaze recording system. In our previous papers we reported a variable error range of 0.7°-10.8° for the Reactive Task and 1.3°-12° for the Memory Delay task, both of which exceed the level of noise in our recording system by more than an order of magnitude. The recording noise would thus show up as small constant residuals in the model fitting algorithm, and thus have little influence on the T-G comparison to comparison between tasks.

4.4 Results

General Observations

Of 86 neurons sampled on-line, we recorded complete datasets (in both the *reactive* and *memory delay task*) from 74 SC neurons from the left and right Superior Colliculus of two head unrestrained monkeys. Of these 54 neurons met all our inclusion criteria (Sajad, Sadeh et al. 2015), including 15 visual, 28 VM and 11 motor neurons (as Identified using the memory delay task; (Sadeh, Sajad et al. 2015).

Figure 2 shows the activity profiles of each category of neurons in our study (Visual, VM, Motor) during gaze saccades to the top 10% data (corresponding to the RF 'hot spot') derived from the *reactive task (red) and memory delay task (black).* Each panel provides mean spike density plots (averaged across neurons ± SEM). Data are aligned both with target onset (Left column; Fig 2 A, C and E) and when aligned with gaze onset (Right Column, Fig 3B, D and F), with the 'fixed-

window' analysis indicated by gray vertical lines and the average duration of the 'full burst analysis' (derived from the reactive task) shown by blue vertical lines. By definition, visual neurons only showed a target-aligned response in the memory delay task (Black data in Fig. 2 A vs. B), whereas VM cells showed both visual and motor responses in both tasks (Fig. 3 C vs. D), and motor neurons only showed peak saccade-aligned responses (Fig. 3 E vs. F). Henceforth we will refer to the data from our fixed target and saccade-related windows as 'visual activity' and 'motor activity', based on their temporal profiles, but later we will use our analysis methods to quantify what spatial parameters these activities encode in different neurons and at different times.

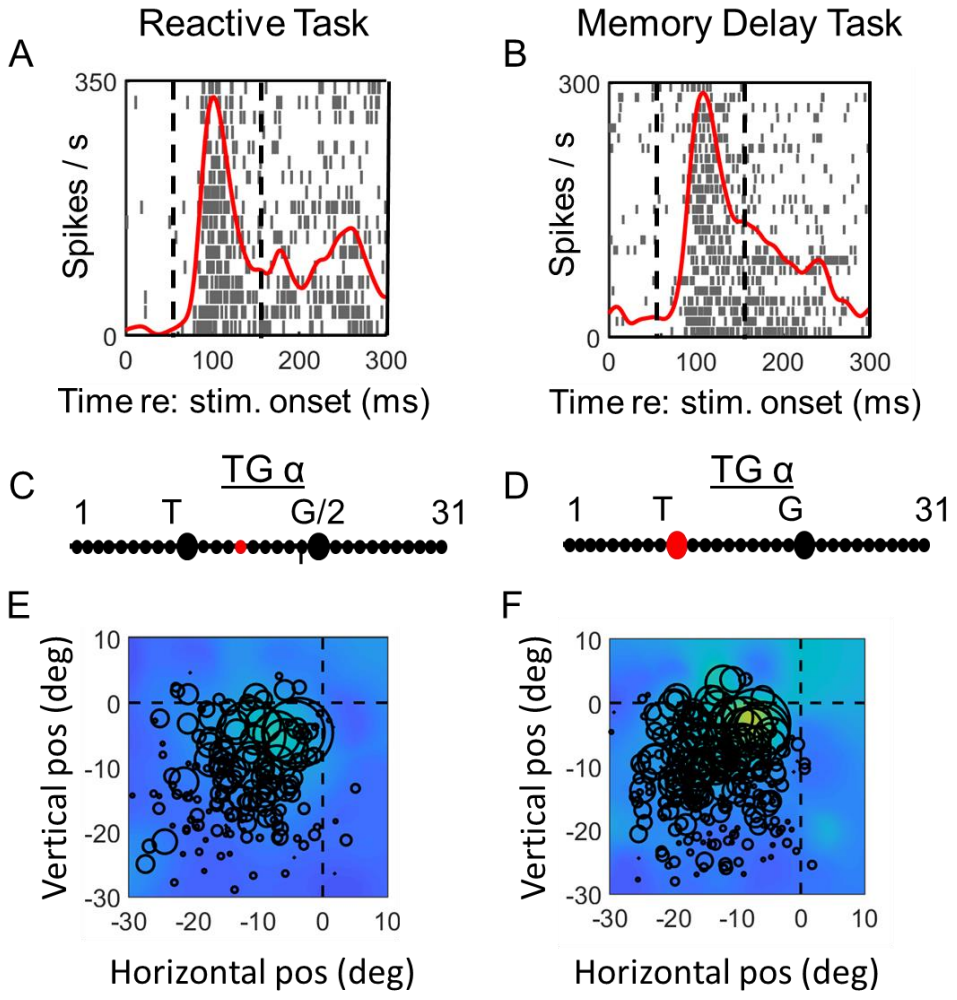

Figure 3: Spatial analysis of *visual* activity during *reactive task* (Left Column) versus *memory delay task* for one example *visual* neuron. *Top row* (A/C): Spike density and raster plot aligned with target onset Vertical dashed lines represent the fixed window of activity which was considered in our visual analysis (60 to 160 ms relative to target presentation). *Second row* (B/D): point of best fit (red dot) on the TG continuum for the response. *Bottom row* (E/F) Response Fields (RF) plotted according to the best TG fit from middle row, note that the circles represent the total number of spikes in the time window for each trial (with larger circles indicating more spikes) and the overall similarity of the circle sizes for a given point in space indicate the coherency and the quality of fit (See materials and Methods). The heat maps in the background represent the non-parametric RF fits made to these data. Thus, lighter colors / larger circles indicate the 'hot spots' of the receptive field.

Temporal Analysis of Reactive versus Memory-Delay Population Activity Profiles

Although our main aim was to compare spatial tuning in neurons between the reactive and memory tasks, we also took the opportunity to compare their temporal firing profiles (Figure 2). (Selected individual examples are provided below in Figures 3, 4, 6, 7.) In general, visual neuron responses (Fig. 2 A) and motor neuron responses (Fig. 2 F) showed similar response profiles in the *reactive* (red) and *memory delay* (black) tasks. However, there were some notable differences such as generally stronger peak activation in the reactive task, followed by a more robust, complex, and prolonged 'tail'. To quantify the degree of response similarity across tasks, we performed a Pearson bivariate two tailed correlations through time on the population activity, and a paired two tailed t-test test to compare the peak top 10% of neural firing rate within the defined windows, in the visual and/or motor alignments as appropriate. Visual neurons (in the visual alignment) showed correlation of 0.934 between the two tasks for the fixed window analysis ($P < 0.0001$) and 0.873 for the full burst analysis ($P < 0.0001$) but the peak activities were significantly higher in the reactive tasks (237 +/- 23 SD vs. 175 +/- 15 SD in *MD* task $P<0.0001$). Motor neurons (in the motor alignment) showed correlation of 0.90 ($P < 0.0001$; fixed window)

and 0.99 (P<0.0001; full burst window) but again had significantly higher firing rate in the in the reactive task (116 +/- 19 SD vs, 100+/- 12 SD in *MD* P<0.0001). Thus, visual and motor profiles were highly correlated between the two tasks, but the peak responses were higher in the reactive task.

In contrast, VM cells (Fig. 2 C, D) showed very different profiles in our two tasks, presumably because the reactive burst contains both visual and motor activity. This is most evident in the visual alignment, where the *memory delay task* yields a burst that aligns well with the initial burst of activity from the *reactive task* data, but the latter shows an additional delayed peak that is presumably the motor response. Further, the visual response in the memory paradigm now seems higher, if anything. In the saccade alignment (D), the reactive task produced heighted earlier activation that could correspond to visual activation, but also a higher and more persistent motor peak that is harder to account for. When we repeated our statistical tests on these data (restricted within the fixed visual and motor temporal windows), we found lower, but still significant correlations in both the visual and motor windows (R= 0.7634 and 0.8164 respectively, with P<0.0001 for both). There was no significant difference in the peaks of activity in the visual window of VM neurons (155 +/- 10 in reactive, 150 +/- 39 in *MD*, p=0.1195), but a significant difference in peak activity in motor window (153 +/- 15 in reactive vs. 103 +/- 14 in the *MD* task, P<0.0001). Thus, if we only look within the fixed visual or motor response windows of VM neurons, they again look somewhat similar and are highly correlated, but with differences in the gain of the motor (not visual) response.

Overall comparing the reactive task to the *MD* task, visual responses showed the same sharp rise but peaked higher in (in visual, not VM neurons), whereas motor responses were higher and more prolonged in both VM and motor neurons. In general, these results were consistent with similar temporal analyses of activity profiles that have been performed previously in head-restrained studies (Goldberg and Wurtz 1972, Wurtz and Goldberg 1972, Sparks 1978, Mays and Sparks 1980, Munoz and Wurtz 1995, Munoz and Wurtz 1995, Dorris, Pare et al. 1997, Everling, Dorris et al. 1999, Gandhi and Katnani 2011), except that, as expected from past studies (Freedman and Sparks 1997, Crawford, Martinez-Trujillo et al. 2003, Stuphorn 2007, Walton, Bechara et al. 2007, Freedman 2008, Sadeh, Wang et al. 2012), our head unrestrained responses were more prolonged and complex

Comparison between Spatial Coding in Reactive versus Memory Delay Tasks: Visual Responses

The preceding temporal analysis suggests both similarities and differences in the Visual and Motor responses to our two tasks, but this itself does not indicate whether the same or different spatial information is being encoded. As noted in the introduction, it is likely that visual and motor responses interact in the *reactive task*, and that suppression and memory signals are present in the *MD* task (White, Sparks et al. 1994, Brown, DeSouza et al. 2004). These factors could affect not only the vigor of the responses (described above) but also their spatial code. To test these various assumptions an independent criterion is required. Here, we did this by using the TG alpha continuum as an independent test of spatial coding in various points of these tasks. Note that for the TG-alpha analysis, all trials were used (not just those to the 'hot spot', so this analysis is based on a much larger, richer dataset.

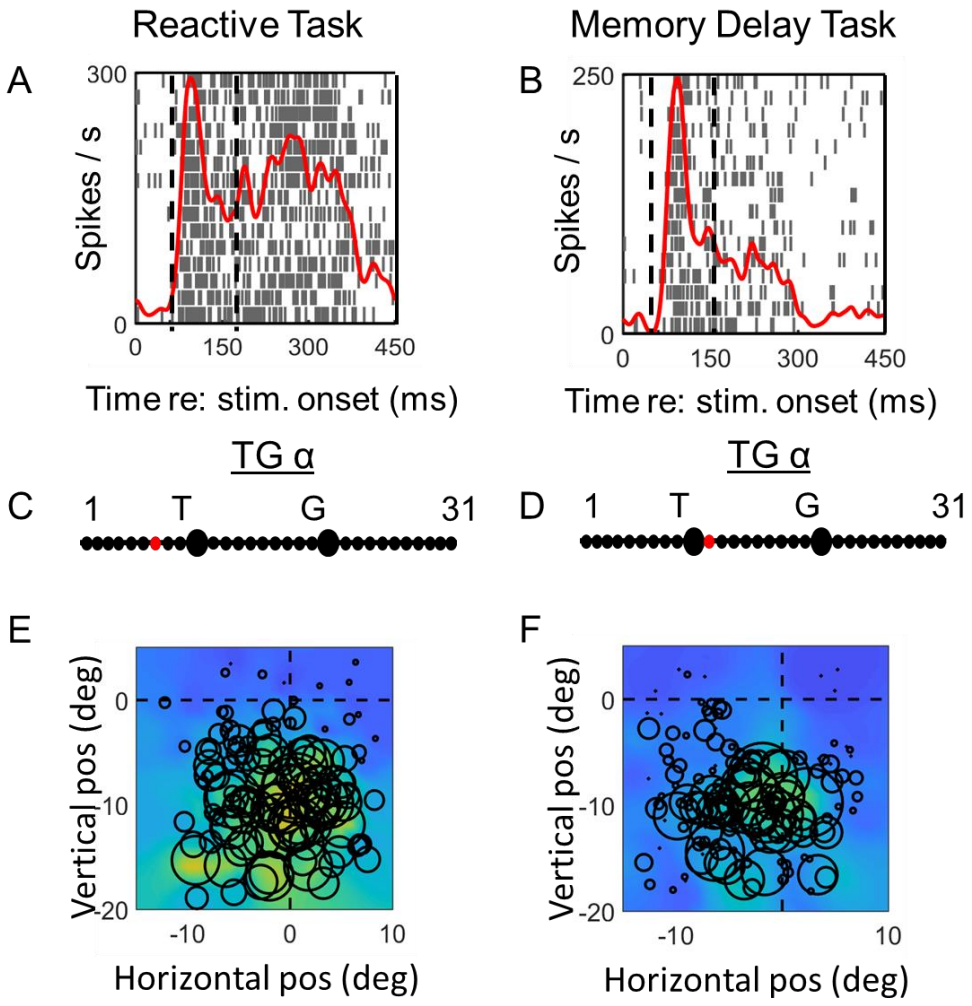

Figure 4: Spatial analysis of *visual* activity during *reactive task* (Left Column) versus *memory delay task* for one example *visuomotor* neuron. The plotting conventions are the same as in Figure 3.

Figures 3 and 4 compares spike density and raster plots (A vs. B), best fits along the TG continuum (C vs. D) and visual receptive fields plotted in these ideal coordinate frames (E vs. F) tested on the same stimulus locations with the reactive task (left column) versus the *MD* task (right column), for an example visual neuron (Figure 3) and the visual response of an example VM neuron (Figure 4). These representative visual neuron raster plot (Figure 3) resembles the population raster seen in figure 2, with a more prolonged burst and a more prominent second

burst in the reactive task. However, the best TG fit for the visual response is shifted leftward toward T in the memory delay task. The overall location and shape of RF remains similar in the two tasks, despite some slight distortions in stimulus location caused by the change in coordinate frame used for the plot. The Visual response of the example VM neuron (Fig. 4) showed similar patterns, except that the relative TG shift was in the opposite direction.

To assess whether these TG shifts followed a pattern (or were randomly distributed across neurons) we compared fits for the two tasks across our entire neuron populations. Figure 5 does this for the visual neurons population (left column), and visual response of the VM population (right column), Providing frequency histograms for TG-alpha fits from the *reactive task* (top row; A, D) and *MD task* (middle row; B, C), recorded from the same neurons. (Recall that TG = 11 denotes a pure target code, whereas 21 denotes a pure gaze code). For this analysis, we used the fixed target-aligned window to compare the two tasks. The mean TG alpha value for visual neurons in the reactive task was 12.2 (SD=4.35) which was not significantly different from 11.87 (SD=2.42) in the memory delay task (p=0.91). This indicates a slight, but not statistically significant, shift toward coding target location in the *MD* task. In the visual activity of VM neurons the same trend (mean reactive: 12.4 SD=3.4, *MD*: 10.9 SD=4.6) is observed with a borderline non-significant (p=0.058) shift toward target coding in the *MD* task.

To directly visualize these comparisons, we plotted the TG alpha values of each neuron in the *MD* task (x axis) and the reactive task (y axis), For the visual neurons (Fig 5E) there is an almost equal number of neurons which do (n=7) and do not (n=8) have different spatial coding between the

tasks, in visual activity of VM neurons (Fig 6F) more neurons (n=21) do not have a change of what spatial info is being encoded in MG vs. the reactive task.

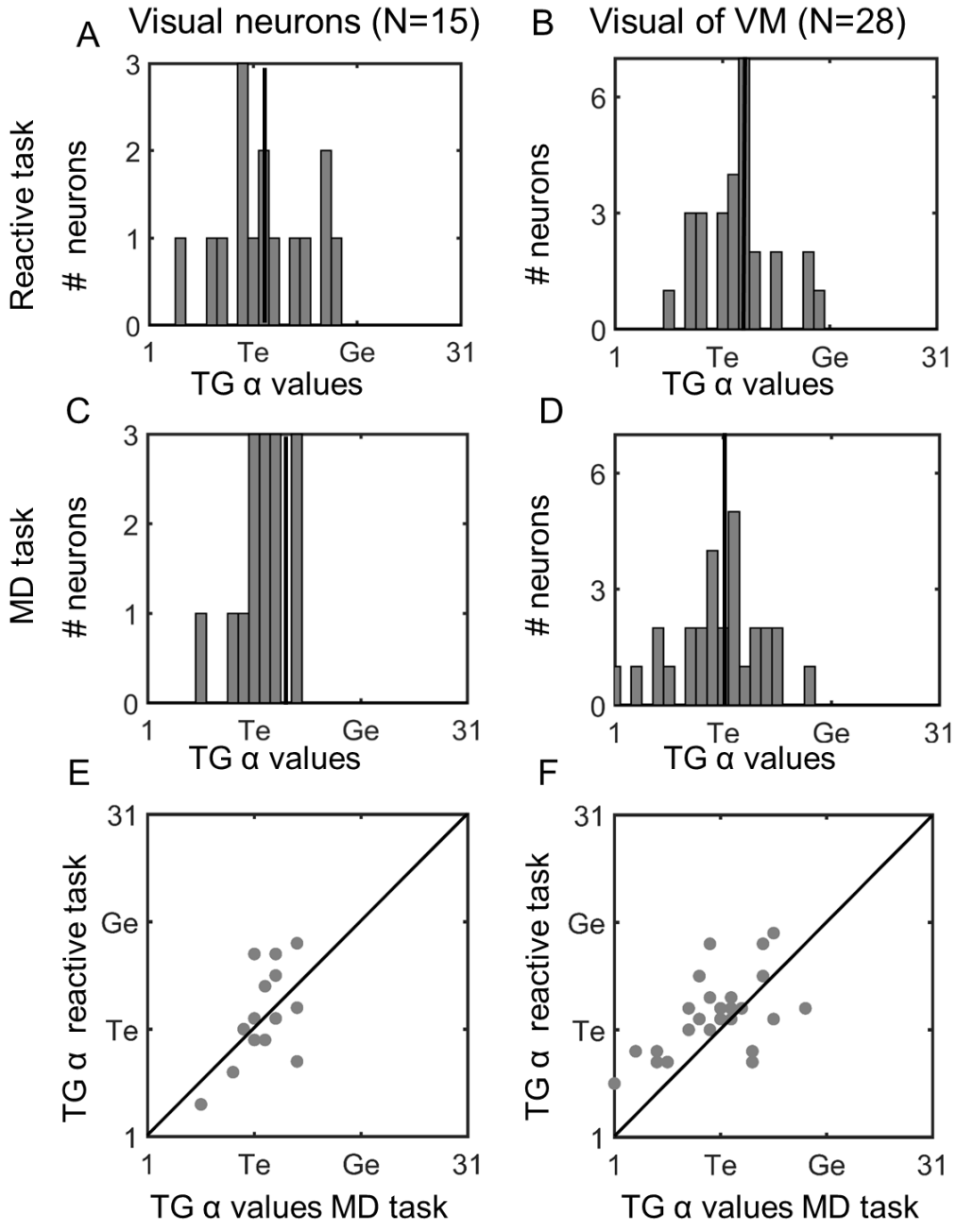

Figure 5: Comparison of TG continuum coding of reactive versus memory delay task in visual responses. *Left column* (A, C, E): Visual Neurons; *Right Column* (B, D, F): Visual response of visuomotor (VM) neurons. Top Row (A, B): TG value distributions in the *reactive task.* Vertical line indicates the median. Second Row (C, D): distributions for same neurons in the memory delay

(MD) task. Visual neurons showed a more restricted distribution, but there was no significant different between the TG values between the two tasks. Bottom Row (E, F) illustrates neuron-by-neuron comparison between the two tasks in the visual activity of Visual and VM neurons respectively, plotting the TG continuum values from the reactive task as a function of the MD task.

When we combined the TG values all the visual activity (i.e. visual neurons and the visual activity of VM neurons) and compared them between the two tasks there is a slight, but not significant (P=0.34), preference for target coding in *MD* (mean TG=11.53 +/- 4.45) compare to reactive task (mean 12.33 +/- 3.73). Finally, there was no significant difference between the goodness of fit (i.e. the mean PRESS residual) of these models to the visual data across all visual and VM neurons in the reactive versus *MD* tasks (P= 0.89). In summary, there was no significant task-dependent difference in spatial coding for the visual responses of the visual and VM neuron populations.

Comparison of Spatial Coding in Reactive versus Memory Delay Tasks: Motor Responses

Figures 6 and 7 (similar to 3 and 4) provide comparisons between the spike density plots, rasters, and non-parametric best fits of motor response fields tested on the same stimulus locations, for the motor response of an example visuomotor neuron (Fig. 6) and motor neuron (Figure 7) respectively. The motor burst of the VM neuron (Fig. 6, top row) illustrates trends seen in the population (Figure 2), being completely separated temporally from the visual burst in the *MD* task (Fig. 6 B) but not the reactive task (Fig. 6 A). For this neuron, the TG fits for the motor response are quite close to T in both tasks (Fig. 6 C, D). As a result, the motor RFs for this neuron (which shows a fairly poor spatial organization) looks nearly identical in both tasks (Fig. 6, E, F).

In the case of the motor neuron example, the TG fit is shifted more toward G in the *MD* task (Fig. 7 C vs. D). As a result, the stimulus locations for the RF plot are slightly compressed in the horizontal dimension for the *MD* data, i.e., because of gaze undershoots in this task. But otherwise, the RFs are similar, showing a downward-leftward preference.

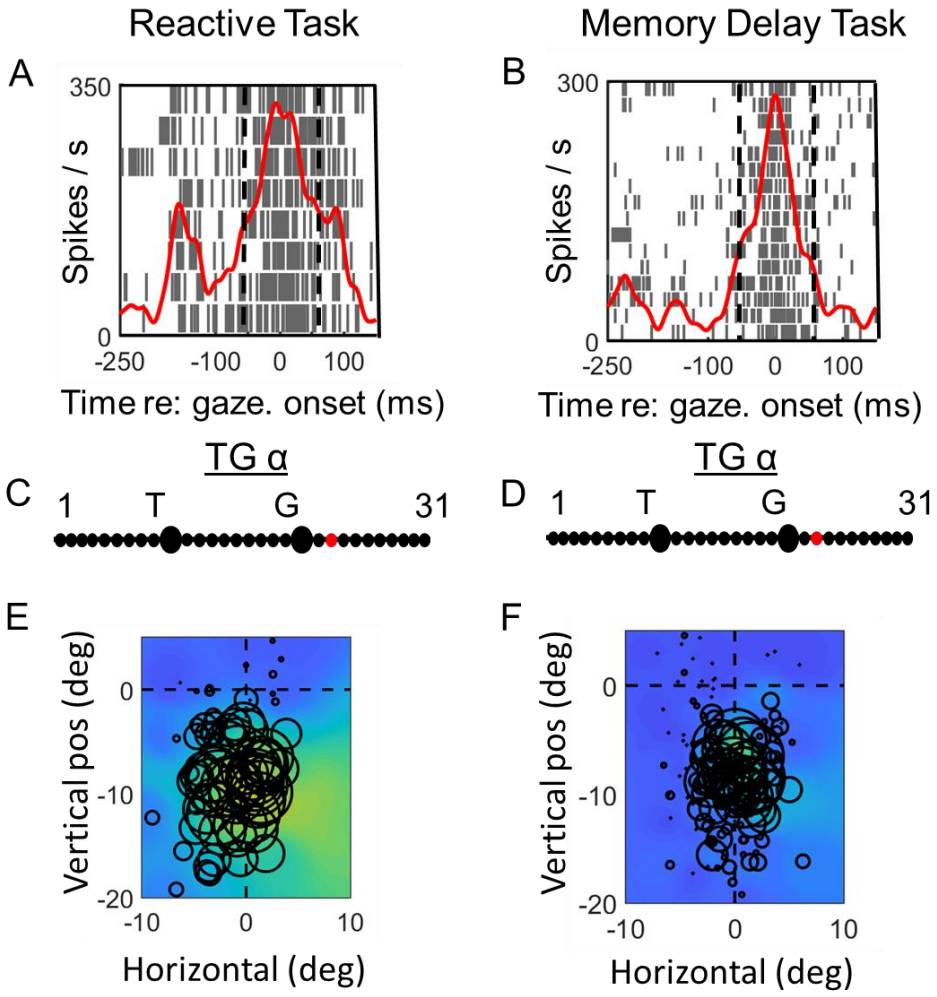

Figure 6: Spatial analysis of *motor* activity during reactive task (Left Column) versus memory delay task for one example *visuomotor* neuron. Vertical dashed lines in A/B represent the fixed motor analysis windows (-50 to + 50 ms relative to gaze onset). Otherwise the plotting conventions are the same as in Figure 3.

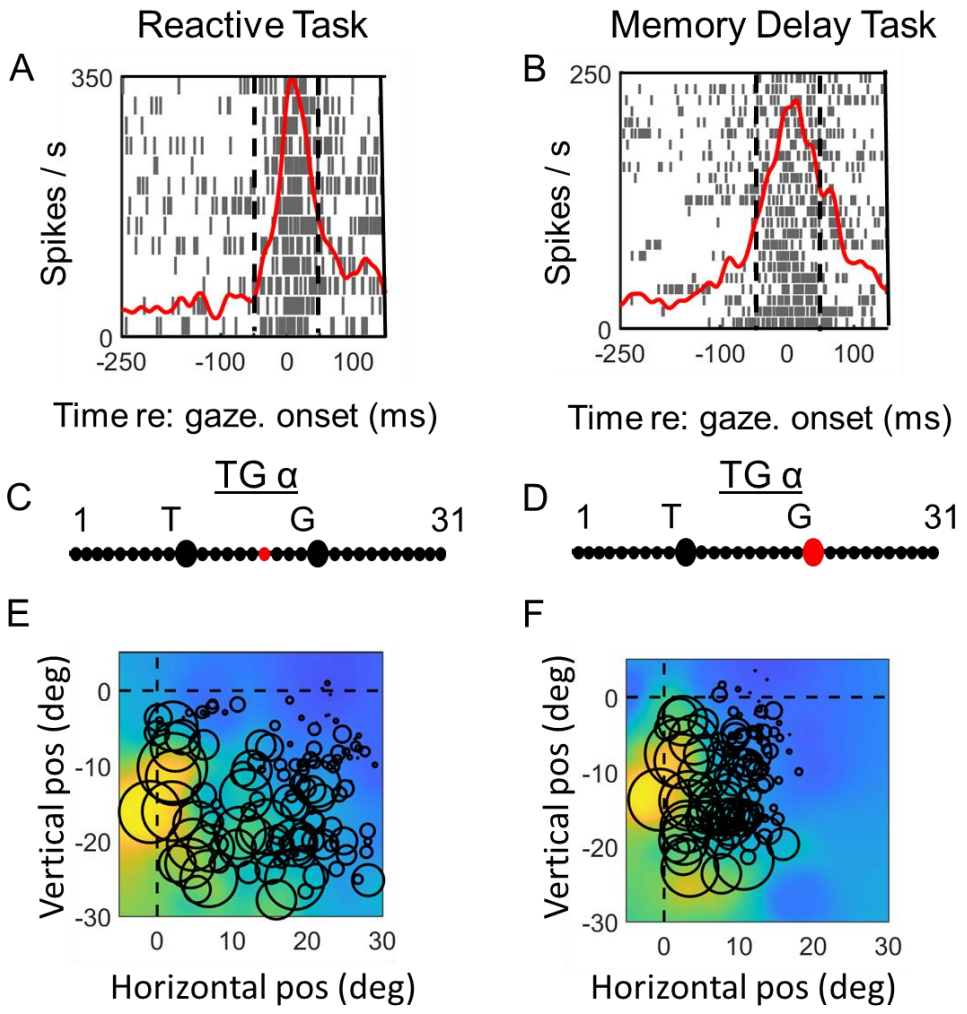

Figure 7: Spatial analysis of *motor* activity during reactive task (Left Column) versus memory delay task for one example *motor* neuron. Vertical dashed lines in A/B represent the fixed motor analysis windows (-50 to + 50 ms relative to gaze onset). Otherwise the plotting conventions are the same as in Figure 3.

Figure 8 (similar to Figure 5) compares the TG alpha values for the fixed window motor responses of VM and Motor Neurons. The motor activity of the VM neurons showed more gaze preference in the *MD* task (mean: 18.3 SD=4.8) than reactive task (mean=17.6 SD=4.9), but this was not significantly different (p=0.58). Interestingly in our pure motor neurons the TG alpha values showed a significantly (p= 0.021, paired t test) more preference (mean: 20 SD=2.29) for

coding the gaze end points in the MG task compare to the reactive task (Mean: 17.2 SD=2.9). This can be visualized in Figure 8 F as a shift in the data from the line of unity, whereas the VM data (Figure 5 E) are evenly distributed across this line.

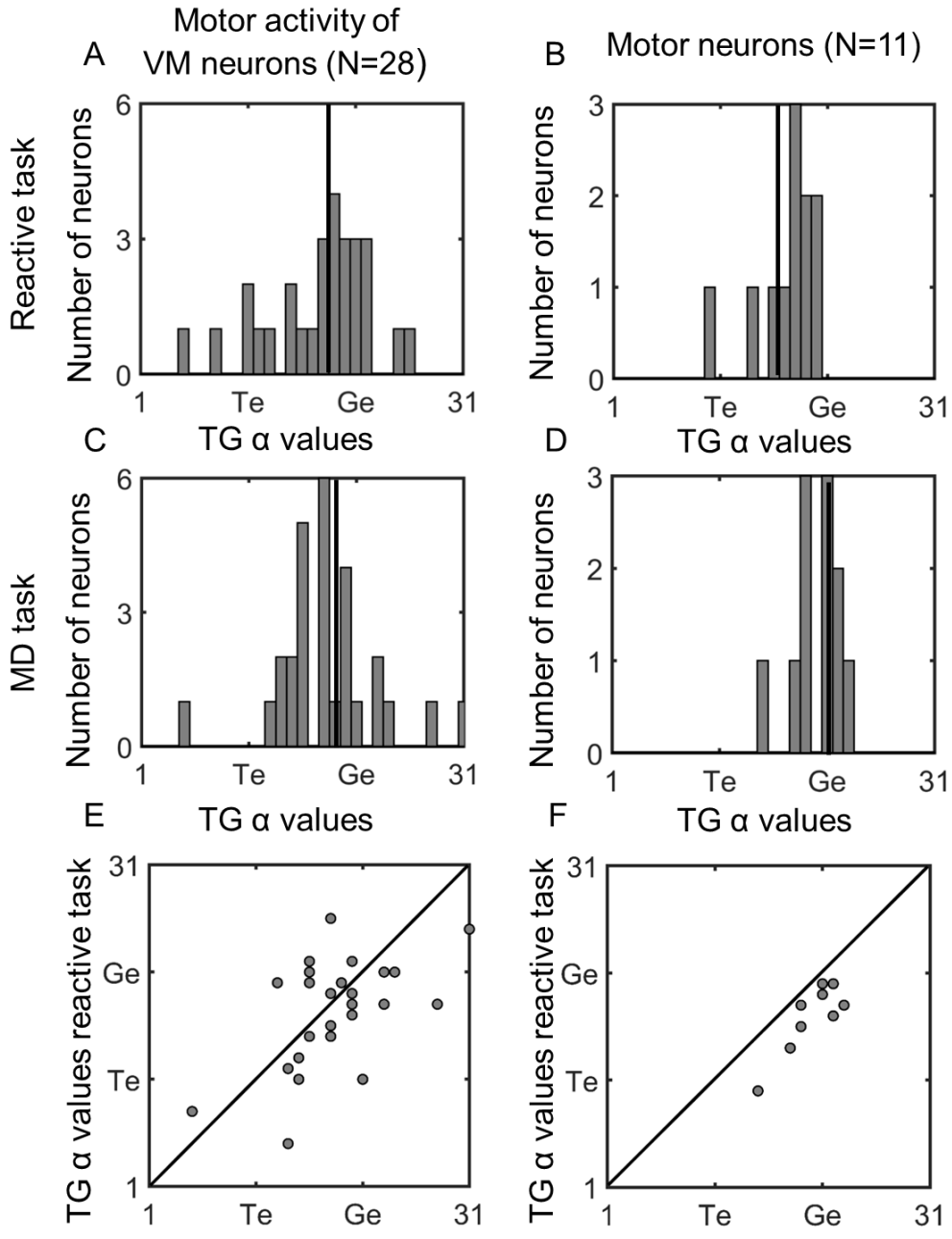

Figure 8: Comparison of TG continuum coding of reactive versus memory delay task in *motor* responses. *Left column* (A, C, E): Motor response of visuomotor (VM) neurons; *Right Column* (B, D, F): Motor response of motor neurons. Otherwise, the conventions are the same as Figure 5.

There was a significant difference between the TG values in the two tasks in Motor Neurons, i.e., the fits were below the diagonal line in part F, meaning motor neurons were more gaze-related in the MD task.

The TG values for the combined motor activity, however, were not significantly different between the two tasks (*MD* task mean =19+/- 4.2, reactive task mean=17.5 +/- 4, P=0.08). In the case of these motor fits, there was a significant increase in the mean PRESS residual across cells (P = 0.03), for the *MD* versus reactive task, possibly because the delay introduced more non-spatial noise in the system. Thus, overall our data tend to confirm the assumption that what is spatially encoded in motor responses of visuomotor neurons is the same regardless of the interposition of a memory delay, but suggests that motor cells show a purer gaze code following a memory delay.

4-5 Discussion

Gaze shifts occur in a variety of circumstances (e.g.: exploring the environment, selecting the stimulus of interest, looking at a suddenly appearing stimulus, etc.) and in each case the number of brain visuomotor areas and the extent of their involvement in generating gaze shifts are different (Dean, Redgrave et al. 1989)Fischer 1986, Gnadt, Bracewell et al. 1991, Pierrot-Deseilligny, Rivaud et al. 1991, Pierrot-Deseilligny, Rivaud et al. 1991, Andersen 1995, Deubel 1995, Schall 1995, Horwitz and Newsome 1999, Hikosaka, Takikawa et al. 2000, Brown, DeSouza et al. 2004, Fecteau and Munoz 2006, Sajad, Sadeh et al. 2016). It is, however, unclear if these differences in the task demands and behavior has any influence in the spatial information encoded by the neurons.

Here we compared the visual and gaze movement related neural activity during head-unrestrained reactive and memory delay gaze tasks in the superior colliculus, a key oculomotor area where many signals from cortex and subcortical areas converge and which directly influences the brainstem premotor neurons that control eye and head rotation (Guitton, Crommelinck et al. 1980, Harris 1980, Sparks and Hartwich-Young 1989, Klier, Wang et al. 2002, Sparks 2002, Klier and Crawford 2003, Walton, Bechara et al. 2007, Gandhi and Katnani 2011). We found both similarities and differences between the overall activity profiles and spatial information encoded by SC neurons between the memory guided and the reactive gaze shifts.

Differences in the timing and vigor of visual and movement related neural responses

By comparing spike density profiles recorded from the same neurons in two different tasks (Fig. 2) we were able to make several noteworthy observations. As expected, the onset and peaks of the visual responses occurred at roughly the same time after target presentation, and the peak of the motor response was similar in both tasks. There was also a strong correlation between the peaks in each task. However, visual neurons showed a higher peak firing rate and all motor responses were higher, as reported in several previous studies (Goldberg and Wurtz 1972, Mays and Sparks 1980, Krauzlis, Lovejoy et al. 2013). This might be accounted for by the presence of saccade suppression signals during the early portion of the *MD* task, and conversely, the presence of visual target and increased bottom-up attention in the reactive task (Desimone and Duncan 1995, Itti 2005, Buschman and Miller 2007).

Effects of offset timing were pronounced in the head-restrained condition, where the visual and motor bursts are already prolonged to accompany the longer duration of the eye + head motion

(Freedman and Sparks 1997, Roy and Cullen 1998, Freedman 2008). For example, the motor burst, already prolonged in head-unrestrained gaze shifts, was even more prolonged in the reactive task than the *MD* task. This and the prolonged, multi-peaked burst activity of visual neurons in reactive task could be attributed to modulations such as attention (Goldberg and Wurtz 1972, Desimone and Duncan 1995, Robinson and Kertzman 1995, Krauzlis, Lovejoy et al. 2013) and motivation (Redgrave, Coizet et al. 2010, Otmakhova, Duzel et al. 2013). Finally, the reactive task trials were shorter so monkeys were rewarded at a higher rate compared to the *MD* task, suggesting that reward signals may have also had an influence (Glimcher and Sparks 1992, Schall 2001, Ikeda and Hikosaka 2003).

These differences in firing could account for differences in speed (Tweed and Vilis 1990, Lefèvre, Quaia et al. 1998, Groh 2001, Sparks 2002), accuracy (Lee, Rohrer et al. 1988, Goldberg and Bruce 1990, Gottlieb and Goldberg 1999) and amplitude (Sparks, Lee et al. 1990, Dorris, Pare et al. 1997, Freedman and Sparks 1997, Freedman and Sparks 1997) reported here and previously in these tasks. The differences in gaze precision reported here (see methods) might be due to lower signal-to-noise ratio in the *MD* firing rates, to related differences in spatial coding, which we will describe more directly in the following sections.

Spatial code differences in visual activity

In both the reactive and *MD* tasks the visual activity preferentially coded for Te, and there was no significant difference between these codes. However, there were subtler differences in the distribution of the TG alpha values of the visual responses between the two tasks (Fig. 5 A vs. C). In visual neurons, the distribution of the TG values was clearly more narrow and clustered around

the Te model in the *MD* task compared to the reactive task (Fig. 5 A vs. C). In VM neurons, the peak of the TG distribution was shifted slightly (although not significantly) toward Te. Overall, this suggests a more faithful coding of the target in visual responses in the *MD* task.

This could be due to an almost simultaneous need for encoding target location as well as preparing for the movement in the reactive task, thus some of the visual responses may have been influenced by movement preparation (Munoz and Wurtz 1993, Dorris, Pare et al. 1997, Horwitz and Newsome 1999, Bell, Meredith et al. 2005) which may shift the spatial information away from the Te model. In the *MD* paradigm when a delay is expected, the visual burst encodes the target location and the signals regarding the movement preparation and from the working memory circuit contribute to the later movement related burst and therefore less intermixing of the activities occurs. This could occur between suprathreshold excitatory motor signals in VM neurons, or through subthreshold or inhibitory motor signals in visual neurons.

Spatial code differences in motor activity

In both tasks, the motor related response of the VM neurons tend to encode spatial information related to gaze endpoint locations rather than target, but this shift toward G coding was more complete in pure motor cells, with closer clustering around the G model in both tasks (Fig. 5 B, D). This is consistent with our previous results from the frontal eye fields, where moto-only cells showed a pure G code (Sadeh, Sajad et al. 2015)Since our method of fitting G is based on fitting variable errors in gaze end points, this suggests that superior colliculus motor responses, particularly in pure motor cells, are casually involved in generating these errors in both tasks, perhaps in communication with other areas like the FEF (Sajad, Sadeh et al. 2015).

Alternatively, pure motor cells may receive feedback from downstream premotor cells that provide a better estimate of actual behavioral output (Waitzman, Ma et al. 1991, Matsuo, Bergeron et al. 2004, Walton, Sparks et al. 2005).

In addition, there was a significantly further shift toward G coding (in pure motor cells) in the *MD* task (Fig. 5 B vs. D, F). Our model normalizes fits relative to the magnitude of errors (Keith et al. 2009; Sajad et al. 2015; Sadeh et al. 2016), but the quality of the fits could have been influenced by signal-to-noise ratio. However, this does not account for why this task-dependence occurred only in motor neurons and not VM neurons. One possible explanation is that by the time motor neurons became active after the memory delay, there was less influence from other neurons with mixed coding on behavior (perhaps through selective gating), and thus an even better relationship between their firing rate and gaze errors. Alternatively, if we consider feedback, it may be that more delay allows a more accurate estimate of output. Other more general explanations will be considered in the next section.

Spatial transformation in reactive and memory delay tasks

In both the reactive and *MD* tasks the general observation is that based on the significantly different TG values, there is a transformation away from coding the location of target to coding the location of gaze end points. In our previous papers we have suggested that this is due to the accumulation of noise in the system(Sadeh, Sajad et al. 2015, Sadeh, Sajad et al. 2018) and as confirmed here, this appears to happen with or without the interposition of a memory delay.

However, despite this similar trend there are some interesting findings which suggest different visuomotor transformation mechanism in each task (Gnadt, Bracewell et al. 1991, Munoz and

Everling 2004, Sajad, Sadeh et al. 2016, Sajad A 2016). As noted above, the visual code represents the target more faithfully in the *MD* task (in terms of overall distribution), whereas the motor response (at least in pure motor cells) more faithfully represents the gaze end point. This would seem to suggest a more perfect transformation, and yet gaze saccades are less accurate and precise after a memory delay in our data and in previous studies (Gnadt, Bracewell et al. 1991, Pierrot-Deseilligny, Rivaud et al. 1991, Stanford and Sparks 1994, White, Sparks et al. 1994).

The answer to this apparent contradiction may be that, despite the rapid mixing of visual and motor signals in the reactive task, at the overall population level the transformation is relatively effective. Second, although the final motor output in the *MD* task faithfully encodes gaze, this includes gaze errors, and the SC (and FEF) is likely one source of these errors, or as suggested above, in the monitoring of those errors as movement progresses.

Finally, the transformation is not necessarily complete at the SC. For example, the TG values of motor activities are significantly different from that for the gaze model, shifted towards the target model, and in the *MD* task they are not. Therefore, it is reasonable to conclude that the SC encodes a gaze goal, which is then subject to further transformations. Errors in those additional transformations could be proportionately larger in the reactive task than the *MD* task, hence the difference in motor code between these tasks. Alternatively, this difference could be attributed to the increase in distribution of errors with time across the entire gaze control system, hence any one area like SC could reflect the gaze errors more closely.

Finally, the current study demonstrates that the model-fitting approach used here is sufficiently robust to identify not only differences in neural codes and transformations (Sajad et al. 2015,

2016; Sadeh et al. 2016; 2018), but also how these depend on brain states. The memory delay interval is known to induce inaccuracies in motor response in a variety of the settings (Postle, Berger et al. 2000, Bays, Gorgoraptis et al. 2011, Barber, Caffo et al. 2013, Chatham and Badre 2015, Hollingworth 2015), but so do other behaviors like express saccades (Pierrot-Deseilligny, Rivaud et al. 1991, Postle, Berger et al. 2000, Corneil, Olivier et al. 2004). More importantly, one would expect such errors to be even larger in clinical disorders (Munoz, Armstrong et al. 2003, Anderson and MacAskill 2013), so this technology might have practical application for detecting quantitative biomarkers in disease states.

Conclusion

In this paper we aimed to provide a comprehensive comparison between the spatial information encoded by visual and motor activities of SC in two different tasks: reactive and memory delay gaze shifts. We found that despite overall similarities in visual to motor transformation, there are several important differences. Most importantly the visual to motor transformation is more extensive in the *MD* task since the TG values in the motor population are closer to gaze models in the *MD* task. This suggests that the brain areas involved in each task contribute to changes in spatial code and ultimately to saccadic errors.

Chapter 5: General Discussion

The process of transforming sensory information into movements routinely occurs in many animals and in humans, and it involves various sensory modalities and movement types, and occurs in various settings. Among these movements, direction of the gaze toward visual stimuli allows for exploration and interaction with the environment, which are essential for survival. In this thesis study, we demonstrated, for the first time, the transformation of visual signals to movement commands in head-unrestrained subjects for both memory guided (Sadeh, Sajad et al. 2015) and reactive gaze shifts. The head-unrestrained setting provides multiple advantages, including allowing an experimental setting which mimicked the natural behaviour more closely, and thus was more applicable (DeSouza, Keith et al. 2011, Sadeh, Sajad et al. 2015, Sajad, Sadeh et al. 2015). It also allowed us to study a broader range of spatial parameters and frames of reference encoded by neurons. Finally, the setting allowed us to investigate whether the neurons were encoding eye movements, head movements, or both (Sadeh, Sajad et al. 2015, Sajad, Sadeh et al. 2015). We also investigated the visual and motor responses separately in two distinct tasks which involve separate neural circuitry (Pierrot-Deseilligny, Rivaud et al. 1991, Pierrot-Deseilligny, Rivaud et al. 1991, White, Sparks et al. 1994, Sommer and Wurtz 2004, Pasternak and Greenlee 2005, Bays, Gorgoraptis et al. 2011, Phongphanphanee, Marino et al. 2014, Sajad, Sadeh et al. 2016), and showed that the different task demands, and thus differences in inputs to the SC neurons, may alter the spatial codes and thus the resulting behaviour as shown by differences in error and accuracy magnitudes in the final goal (Gnadt, Bracewell et al. 1991). The possibility of a continuous transformation was also investigated by examining the time epochs

during the reactive saccade task to show that in each progressive time there was a change in the spatial information encoded by the neural population, thus supporting a stepwise visuomotor transformation. In the discussion, we review our findings in more detail, and explain how these findings fit into the existing models to contribute to our further understanding of the mechanism of visual-to-movement transformation in the brain gaze control system (Optican 1995, Sajad, Sadeh et al. 2016).

5.1 Eye and head movements

Several mechanisms for the control of coordinated eye and head movements have been proposed, and in most, the SC neurons play a central role as the input providers for the downstream eye and neck muscle nuclei in the brainstem (Guitton, Crommelinck et al. 1980, Harris 1980, Guitton, Munoz et al. 1990, Fuller 1992, Freedman and Sparks 1997, Crawford, Martinez-Trujillo et al. 2003, Klier and Crawford 2003, Klier, Wang et al. 2003, Chen and Walton 2005, Chen 2006, Stuphorn 2007, Walton, Bechara et al. 2007, Freedman 2008, Monteon, Wang et al. 2013). However, whether these signals act as separate inputs for head and eye movements that diverge as they exit the SC output layer, or whether they are a combined eye plus head command, which will separate within their appropriate nuclei, is still debatable. The evidence that there are neurons that are specifically responsive to head movements only (Crawford, Martinez-Trujillo et al. 2003, Stuphorn 2007, Walton, Bechara et al. 2007) provides some basis for the SC providing direct input to head movement nuclei. However, these neurons lack any specific receptive fields for head movements (Gandhi and Katnani 2011), and several previous studies have shown that SC stimulation (Guitton, Crommelinck et al. 1980, Guitton, Munoz et al.

1990, Klier, Wang et al. 2001, Klier and Crawford 2003) and recording (Sparks and Hartwich-Young 1989, Freedman and Sparks 1997, Freedman and Sparks 1997) results in coordinated eye and head movements. Therefore, the evidence for the combined gaze code tends to outweigh the evidence for separate coding for each effector. Similarly, in our study, we found that the motor-related activity of our neuronal population preferentially encoded gaze movements rather than eye or head displacements alone. Although there were a few cases in which the preference in coding head versus eye or gaze was not significantly separated, this difference was clear and statistically significant at the population level in both the memory delay (MD) and reactive gaze shifts. However, to directly address this question, a separate set of experiments with tasks designed to create a considerable separation between head and eye movements and recordings from other possible areas in the brainstem are needed (Sparks and Hartwich-Young 1989, Freedman and Sparks 1997, Sparks 2002, Crawford, Martinez-Trujillo et al. 2003, Klier and Crawford 2003, Klier, Wang et al. 2003, Freedman and Quessy 2004, Quessy and Freedman 2004, Freedman 2008, Sadeh, Sajad et al. 2015).

5.2 Frames of reference (FoR) in the SC

Understanding the FoR in the brain is central to determining the spatial information encoded by the brain and its transformation of information. Multiple studies have shown that the dominant frame of reference in most visuomotor pathways is eye centred (Sparks 1989, Groh and Sparks 1992, Soechting and Flanders 1992, Cohen and Andersen 2000, Klier, Wang et al. 2001, Cohen and Andersen 2002, Martinez-Trujillo, Medendorp et al. 2004, Avillac, Deneve et al.

2005, Constantin, Wang et al. 2007, DeSouza, Keith et al. 2011, Sadeh, Wang et al. 2012, Monteon, Wang et al. 2013). The SC is no exception, with both recording and stimulation studies providing significant evidence for an eye-centred FoR in the SC. In our study, we found that the eye-centred FoR was consistently preferred in both visual and motor activity across all neuron types, and there was no change in preference despite the change in spatial code. We also did not find any changes in the FoR between MD and reactive tasks, and for both, the eye remained the predominant FoR for encoding spatial parameters, even when we studied the time epochs between visual and motor bursts during the reactive tasks (Sajad, Sadeh et al. 2016). Therefore, the possible FoR transformation required for successful visual to motor transformation probably occurs at downstream levels, perhaps at the oculomotor and head movement nuclei (Sparks and Hartwich-Young 1989, Schlag and Schlag-Rey 1992, Cowie and Robinson 1994, Pouget and Snyder 2000, Snyder 2000, Klier, Henriques et al. 2002, Sparks 2002, Crawford, Martinez-Trujillo et al. 2003, Gandhi and Katnani 2011, Sajad, Sadeh et al. 2016). In this study, we introduced significant random variation in the initial position and used a completely head-unrestrained setting, which showed that the SC encoded both target location and gaze commands in eye-centred coordinates. In our intermediate model analyses, we did not find any preference for head- or space-centred FoR, but rather, we showed that most of the visual and movement responses had FoR closely described by the eye frame. These results suggested that the transformation of a common gaze signal into individual eye/head codes and coordinate transformations did not occur in the SC (Freedman and Sparks 1997, Freedman 2008).

5.3 Visual and motor spatial codes and transformations

The biological basis of essentially any type of movement is transformation of neural signals into commands for movements (Hebb, Martinez et al. 1994), whether these signals are driven by internal (e.g., cognition) (Georgopoulos 2000, Musallam, Corneil et al. 2004) or external (e.g., visual or auditory) (Gnadt, Bracewell et al. 1991, Pouget and Snyder 2000, Porter and Groh 2006, Marino, Rodgers et al. 2008, Hawkins, Sayegh et al. 2013, Sadeh, Sajad et al. 2015, Sajad, Sadeh et al. 2015) stimuli. We focused on the latter to study the transformation of visual stimuli into commands for eye and head movements toward the stimuli. Spatial transformation is needed because successful gaze movement information regarding the stimulus location needs to be transformed into a signal for muscle contraction so that the final gaze position relocates the stimulus of interest onto the fovea (Sparks 1989, Stanford and Sparks 1994, Crawford and Guitton 1997, Sommer and Wurtz 2004, Sommer and Wurtz 2004). Nevertheless, the final gaze position is not necessarily the exact same location as the stimulus because of inherent errors in behavioural and task-dependent errors (Stanford and Sparks 1994, Krauzlis, Basso et al. 1997, Noto and Robinson 2001), which may dissociate the final gaze and target locations even further (Keith, DeSouza et al. 2009, DeSouza, Keith et al. 2011, Sadeh, Sajad et al. 2015, Sajad, Sadeh et al. 2015). In our study, we investigated the transformation of visual responses to motor responses of the SC neurons, both between and within individual neuron types, and in two different tasks: MD and reactive gaze shifts.

To our knowledge, this study was the first to simultaneously investigate 11 possible spatial codes for SC activity in both visual and motor activities, and in separate neuron types. By separating the visual and motor responses using a MD paradigm, we showed that there was a

significant change in coding of the target location in eye-centred FoR to final gaze positions, which were also in the eye frame of reference. Thus, we concluded that there was a transformation between the input to output signals of the SC. Moreover, there was also a transformation in the individual visuomotor neurons when their visual and motor activities were analyzed separately (Keith, DeSouza et al. 2009, DeSouza, Keith et al. 2011, Sadeh, Sajad et al. 2015). This data provided significant evidence supporting other studies' findings that the SC has a direct and prominent role in determining retinal error (Sparks 1978, Wurtz and Albano 1980, Waitzman, Ma et al. 1988, Sparks 1989, Sparks and Hartwich-Young 1989) and transforming it into the movement goal (i.e., the final gaze position at the output layer) (Mays and Sparks 1980, Stanford and Sparks 1994, Vogelbaum 2005, Sadeh, Sajad et al. 2015). The latter showed a clearly significant preference for coding the final gaze position of the motor neurons, which are considered the output providers of the SC. Although several studies proposed that the SC encoded the retinal error and displacement vector, rather than the final gaze position, our evidence suggested otherwise. Moreover, by comparing the spatial information encoded by motor neurons in the MD and reactive tasks, we found that the general trend of transformation stayed the same, such that in both tasks the visual activity encoded the target location, and in later motor-related activities, the spatial code changed to predominantly the final gaze position. Therefore, the possible changes in input sources and the weight of those inputs between the tasks did not have a significant effect on the overall spatial codes of visual and motor activities in the SC. However, there were interesting differences between individual neuron types and the extent of the transformation, which will be discussed in more detail (see "*Task demands and changes to spatial transformation*").

5.4 Changes of spatial codes in reactive tasks through time

Based on our findings that the visual and motor activity in the SC coded for two different spatial models, which reflected a sensorimotor transformation that happened both within and between the neurons, we investigated how these transformations occurred. More specifically, we were interested in knowing whether there is a gradual, stepwise, or abrupt transformation, as this could provide more information regarding how the neural activity was encoding each spatial information set. Previously, Sajad and colleagues (Sajad, Sadeh et al. 2016) showed that in FEF neurons, there was a gradual overall shift in the spatial code from the target model to the gaze model during memory guided saccades. This shift was significant, and when the delay period was broken down into equal time epochs, each subsequent epoch showed a stepwise shift in spatial code from the target to gaze model (Sajad, Sadeh et al. 2016). An explanation for this shift was proposed by Sajad and colleagues (Sajad, Sadeh et al. 2016) suggesting that the working memory representation of the target is retrieved into a relatively inaccurate presentation relative to the actual target location, which translates into a final gaze command that is, in turn, the gaze model. Hence, the gradual transformation of target to gaze was attributed mainly to the working memory noise. Similar studies also have shown that the working memory network influences movement predominantly by introducing errors in accuracy (Gnadt, Bracewell et al. 1991, Stanford and Sparks 1994, Goldman-Rakic 1995, Miller, Erickson et al. 1996, Henriques, Klier et al. 1998, Pesaran, Pezaris et al. 2002, Sajad, Sadeh et al. 2015). In our study, we showed that a similar trend of a gradual shift in visual-to-movement transformation occurred in the reactive task when the entire activity during the reactive saccades was broken down into seven time-normalized windows (Sajad, Sadeh et al. 2015). Although the role of working memory in reactive

tasks is considerably less than in a MD task because the target of the gaze is visible at the time of the final gaze positioning, we still observed a similar pattern of target to gaze transformation even during a very short period of gaze movement. Regarding the SC motor activity coding for the final position goal of the gaze rather than retinal error (Waitzman, Ma et al. 1988, Optican 1995, Freedman and Sparks 1997, Sparks 2002), the target to gaze transformation still needed to occur for a successful generation of final gaze commands based on the location of target, as coded by motor and visual activities (Sadeh, Sajad et al. 2015). In addition, our findings in the time epoch analyses indicated that this transformation occurred in a similar manner throughout the activity in the reactive task, and therefore, the entire mechanism of visual to motor transformation also happened independently in the SC. Nevertheless, because of the lack of significant involvement of working memory, the extent of the shift was less compared to the delay tasks, which may explain the role of working memory noise in inducing errors in the final gaze position (see "*Task demands and changes to spatial transformation*").

5.5 Task differences and changes in spatial transformation

The extent and diversity of SC inputs and outputs have been well studied in both anatomical (Sparks 1978, Wurtz and Albano 1980, Moschovakis, Karabelas et al. 1988, Moschovakis, Karabelas et al. 1988, Sparks and Hartwich-Young 1989) and electrophysiological studies (Benevento and Fallon 1975, Cowie and Robinson 1994, Sommer and Wurtz 2002, Sommer and Wurtz 2004). It is also probable that there are changes in the input sources depending on the tasks involved. Therefore, it is plausible that the spatial information encoded by the SC in different tasks also changes under the influence of task demands and changes in

inputs (Sparks 1978, Moschovakis, Karabelas et al. 1988, Moschovakis, Karabelas et al. 1988, Glimcher and Sparks 1992, Sommer and Wurtz 2002, Ignashchenkova, Dicke et al. 2004, Gandhi and Katnani 2011, Phongphanphanee, Marino et al. 2014). Here, we have recorded the activity of the same neurons during reactive and MD tasks, which are highly likely to have different input types based on previous findings, further suggesting different brain mechanisms for generating each type of gaze shift (Everling and Munoz 2000, Corneil, Olivier et al. 2004, Alahyane, Salemme et al. 2007, Kastner, DeSimone et al. 2007, Barber, Caffo et al. 2013). We found that during both the MD and reactive saccades, there was a significant spatial code transformation between and within the neurons, thus suggesting that the role of the SC in transforming visual signals into the determination of the final location of the gaze shift was independent of the tasks and probably the inputs involved. However, we found that the shift from the target spatial code to gaze spatial code was more prominent in the MD task based on the following: 1) the result of the Wilcoxon *t* test in the reactive task, which showed that the TG alpha value of motor activity in the reactive task was significantly less than the arbitrary value of 21 chosen as the gaze coding in our target to gaze continuum, was not significantly different in the MD task; and 2) the TG values of all activities between the reactive and MD tasks were not significantly different, except for the motor neuron population, which is the output layer of the SC (Sparks 1978, Wurtz and Albano 1980, Sparks and Hartwich-Young 1989). Together, these results suggest that in the MD task there was a more dramatic target to gaze spatial transformation. In other words, the spatial code of the motor activity in the MD task was farther away from the target presentation (i.e., was more gaze related), and this was especially true in the motor neurons. In addition, we found a greater error in our MD task compared to the reactive task, which further explains the

dissociation between target and gaze coding in the reactive task. These results further suggest that the working memory input from higher cortical areas, which was more prominent during the MD task, introduced a noise that resulted in a less accurate representation of the target at the output level, and thus, a spatial code more closely related to final gaze position rather than target. This implies that the retrieved remembered location of the target was coded as the final gaze position and was less accurate (Ploner, Rivaud-Pechoux et al. 1999, Brown, DeSouza et al. 2004, Kastner, DeSimone et al. 2007, Bays, Gorgoraptis et al. 2011, Barber, Caffo et al. 2013) than the target representation in the reactive task.

5.6 Clinical Implications

Understanding the neural correlates of visual to motor transformation is essential for understanding the conditions that lead to disruption in neural behaviours. For example, initiation of movement, including saccadic eye movements, is very difficult for patients with Parkinson's disease. In particular, movement initiation toward visual targets is delayed and shows significantly lower reaction and movement times (Gaymard and Pierrot-Deseilligny 1999, Vidailhet, Rivaud et al. 1999, Chan, Armstrong et al. 2005). Therefore, understanding the mechanism of visual-to-movement transformation and the basal ganglia to the SC and other visuomotor pathways (Parent and Hazrati 1995, Hikosaka, Takikawa et al. 2000, Watanabe and Munoz 2011) can provide invaluable insights regarding how the transformation is disrupted, and this information can further provide clues for diagnostic and possible deep brain stimulation treatment targets (Basso, Powers et al. 1996, Aziz and Bain 1999, Lozano, Dostrovsky et al. 2002, Kells, Eberling et al. 2010, Terao, Fukuda et al. 2011). In schizophrenia, the connection between the limbic system and BG is disrupted, and the subsequent BG outputs to the gaze systems are

affected which leads to movement difficulties including volitional eye movements. Understanding the pathway of sensory to movement transformation can lead to new insights concerning the pathophysiology of movement manifestations of schizophrenia (Fukushima, Fukushima et al. 1988, Fukushima, Morita et al. 1990, Parent and Hazrati 1995, Ross, Harris et al. 2000). The working memory process is also interrupted in many conditions, especially in attention deficit hyperactivity disorder (ADHD), and the distractibility and working memory load are components of tests of variable attention (TOVA), which are used for the diagnosis and evaluation of ADHD. The findings regarding the impact of working memory in movement errors can be used both to develop diagnostic tools and to further understand the neurological basis of this condition (Borger and van der Meere 2000, Ross, Harris et al. 2000, Munoz, Armstrong et al. 2003, Rommelse, Van der Stigchel et al. 2008). Finally, understanding the neural signals and the correlates of what they represent or encode is essential for the development of brain/machine interfaces (BMI) (Lebedev and Nicolelis 2006). One of the BMI devices that has shown promise for providing alternative means for movement in disabled patients is a neural prosthetics, which uses brain signals originating from the implanted electrodes in the brain to move a robotic limb (Schwartz, Cui et al. 2006). This requires a thorough understanding of neural signals, including the information being encoded as well as what the frequency, temporal changes, and synchronization of activities present (Musallam, Corneil et al. 2004, Ojakangas, Shaikhouni et al. 2006, Schwartz, Cui et al. 2006, Tam, So et al. 2015). To date, several successful experiments in animal models and human patients showed promising results using signals from motor areas of the brain to control robotic arms (Hochberg, Serruya et al. 2006, McKhann 2008, Velliste, Perel et al. 2008, Hochberg, Bacher et al. 2012, Kingwell 2012). Therefore, a further understanding of

neural signals may help in the development of BMI to transform sensory or cognitive signals into purposeful movements (Normann, Maynard et al. 1999, Pesaran, Musallam et al. 2006, Andersen, Hwang et al. 2010).

5.7 Limitations and future directions

Understanding the biological basis of the mechanisms of brain generating behaviour is of extreme importance. Many areas of the brain are involved in processing this information, but many unanswered questions remain. Despite our best efforts to create an experimental setting to answer as many questions in our studies as possible, it is inevitable that there were limitations to this study. For example, our experiments were designed to mimic a natural setting of MD and reactive gaze shifts as closely as was permitted in a controlled laboratory setting. Thus, we were not able to utilize behavioural circumstances that required considerable dissociation between the eye and head movements or gaze shifts that had large amplitudes (Freedman and Sparks 1997, Freedman and Sparks 1997, Stuphorn 2007, Walton, Bechara et al. 2007, Gandhi and Katnani 2011). This limited the establishment of a definite correlation between SC activity and eye versus head movements. Nevertheless, our aim in this study was to investigate the spatial codes as they occurred in normal gaze shifts, and to this end, the behaviours we observed helped accomplish our goals. Moreover, in our MD task, we did not specifically examine the effects of MD lengths on the accuracy of performances and the changes in spatial codes. The variable MD was used only to minimize the anticipation effects in subjects; however, in the future, the effects of different MD lengths on spatial codes should be further investigated (Goldman-Rakic 1995, Pasternak and Greenlee 2005, Bays, Gorgoraptis et al. 2011, Chatham and Badre 2015, Funahashi

2017). In addition, our experimental tasks were designed to independently investigate the spatial codes utilized by neurons in each of the tasks, and were not meant as a direct comparison. Although our data provide an invaluable basis for an overall comparison of the spatial codes between the two tasks, which has never been done to the same extent and in the same settings, the data could not provide any type of correlation of the spatial codes. Moreover, our interpretation of the possible sources of error in the MD task, and the possible neural substrates that accounted for the differences in the spatial codes, were based on previous anatomical and electrophysiological studies (Sparks 1978, Moschovakis, Karabelas et al. 1988, Moschovakis, Karabelas et al. 1988, Sparks and Hartwich-Young 1989, Munoz and Wurtz 1995, Munoz and Wurtz 1995, Sommer and Wurtz 2002, Sommer and Wurtz 2004, Sommer and Wurtz 2004). Thus, the connections and effects and our interpretations are an extension of the currently published data. We also did not divide the reactive saccade into various subtypes, such as express saccades or overlapping saccades, which are also proposed to have different mechanisms of generation in terms of inputs and outputs (Fischer 1986, Weber, Latanov et al. 1993, Munoz and Wurtz 1995, Munoz and Wurtz 1995, Corneil, Olivier et al. 2004). However, these behaviours and their spatial codes should be investigated in future studies.

Conclusions

This dissertation project aimed to provide further understanding of the mechanisms of an important and fundamental process, sensory to movement transformation. By recording the activity of neurons in the SC, and correlating activity with the behaviour of the subjects, we showed that the signals encoded by these activities evolved from visual to movement-related signals, a process that is seen both between and within the individual neural activities in corresponding visual and movement related responses. Furthermore, we found that the neural activity representing the visual-to-movement activity occurred both during a task that involved a memory gap between the stimulus representation and the movement initiation, as well as during the reactive gaze movement task. However, we observed differences both in behaviour and the extent of visual-to-movement transformation between the two tasks. Taken together, these data suggest that the process of visual-to-movement transformation, which is essential for our interaction with and exploration of the environment, occurred in the SC independent of the task, and that the final output of the SC represented the final position of the gaze, demonstrating an active transformation rather than a passive relay of retinal error signals from the input level. Finally, the task differences seen in both the behaviour and spatial code changes between the two tasks may reflect changes in the influence of the inputs, namely the working memory circuit, which is probably more prominent in the MD task.

Candidate Contribution

The candidate (Morteza Sadeh) was involved in all stages of the experimental work, including experiment design, data acquisition, animal training, data analysis and the write up of the manuscripts presented in this dissertation. This would have not been possible without the help of the co-authors:

Drs. Amirsaman Sajad, Hongying Wang, Xiaogang Yan and assisted with training the subjects, surgery and early phases of the collection of data that's presented in this dissertation.

Dr. Gerald P Keith contributed to the development of the model-fitting method (Keith et al., 2009; also used in DeSouza et al., 2011 and Sadeh et al., 2015) used throughout these studies. This method was further elaborated by the candidate and Dr. Sajad to consider additional coding schemes critical for the primary conclusions on this dissertation.

Prof J.D. Crawford supervised the project and provided critical input and guidance into designing the studies conducted in this dissertation, presenting the data, and the write up of the manuscripts.

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